Estimation of relative bilateral renal function of potential voluntary kidney donors using various computerized tomography methods.

A dissertation submitted in partial fulfillment of MD Radiodiagnosis (Branch VIII) examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2014

CERTIFICATE

This is to certify that the dissertation entitled “Estimation of relative bilateral renal function of potential voluntary kidney donors using various computerized tomography methods” is the bonafide original work of Dr.K.RagulSiddarth submitted in partial fulfillment of the requirement for MD Radiodiagnosis (Branch VIII) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2014.

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My wife, parents and brother for their love, constant support and encouragement.

I dedicate this dissertation to my little daughter Nivi who is always an infinite source of happiness to me.

CONTENTS

AIM

Estimation of relative bilateral renal function of potential voluntary kidney donors using various computerized tomography methods.

OBJECTIVES

a) To estimate relative renal function by four different methods in live voluntary kidney donors using computed tomography.

    1. Semi-automated volume method
    2. Attenuation capacity method
    3. Modified ellipsoid method
    4. Parenchymal area method.

b) To compare the results of relative renal function estimated by the four CT methods with that estimated by Tc99m DTPA renal scintigraphy to identify the best fit CT method to determine split renal function.

INTRODUCTION

End stage renal disease is a common disease entity. Diabetes mellitus and hypertension are the most common diseases that cause end stage renal disease. The functional units of the kidneys are the nephrons. In progressive renal failure, the nephrons have an inherent capacity to function normally for many years.

But as the process of end stage renal disease evolves the nephrons are destroyed one by one. Eventually there is a stage where only twenty percentage of the nephrons function normally.

Further damage occurs in the form of theremaining nephrons undergoing compensatory hypertrophic changes. Eventually it results in termination of the abnormal nephrons.Beyond this stage the symptoms of renal disease begin to manifest. The varied symptoms of renal failure constitute uremia.

Various treatment options are there for a person with endstage renal disease. Initially the patient is managed with dietary modifications and medications. But when these are inadequate to prevent uremic symptoms then only two options remain which are dialysis and kidney transplantation.

Dialysis is further divided into chronic ambulatory peritoneal dialysis (CAPD) and intermittent haemodialysis. In CAPD the peritoneum acts as the membrane for filtration but this method is employed only for minority of the patients.

Most others are subjected to intermittent hemodialysis. This method involves extracorporeal circulation. Here the filtration happens through an external filter. This method is considered an active treatment for patients in uremia and is much more efficient than CAPD. However they are associated with severe lifestyle limitations. There is also severe reduction in life expectancy (1).

The definitive treatment option for end stage renal disease is renal transplantation (2). Live donor kidney transplantation is the most common form of transplantation done in India. Live kidney donation is better than cadaveric transplants as the surgical procedure can be performed electively which has resulted in increased survival benefits as compared to cadaveric transplants.

PRESENT KNOWLEDGE AND REVIEW OF LITERATURE

THE LIVING RENAL DONOR

The living renal donor is actually one of the very few subjects in the healthcare network that cannot be called patients and are actually healthy volunteers. As with any medical or surgical intervention there must be a careful analysis of the risk versus benefit ratio. However for a living renal donor there are no direct personal benefits but the risks and inconveniences of a surgical procedure are very much there.

Therefore itis important to ensure that the donor does not suffer harm as a result of donation. Hence assessing relative renal function is an integral and critical part of the preoperative workup before a renal transplantation surgery. The most crucial aspect is not to leave the donor with a single poorly functioning kidney.

ANATOMY OF THE KIDNEYS

The anatomy of the kidneys can be further divided into gross anatomy of the entire organ and microanatomy of the kidneys internal architecture. The microanatomy of the kidney predominantly deals with the structure of the nephrons which are considered the functional unit of the kidneys.

GROSS ANATOMY

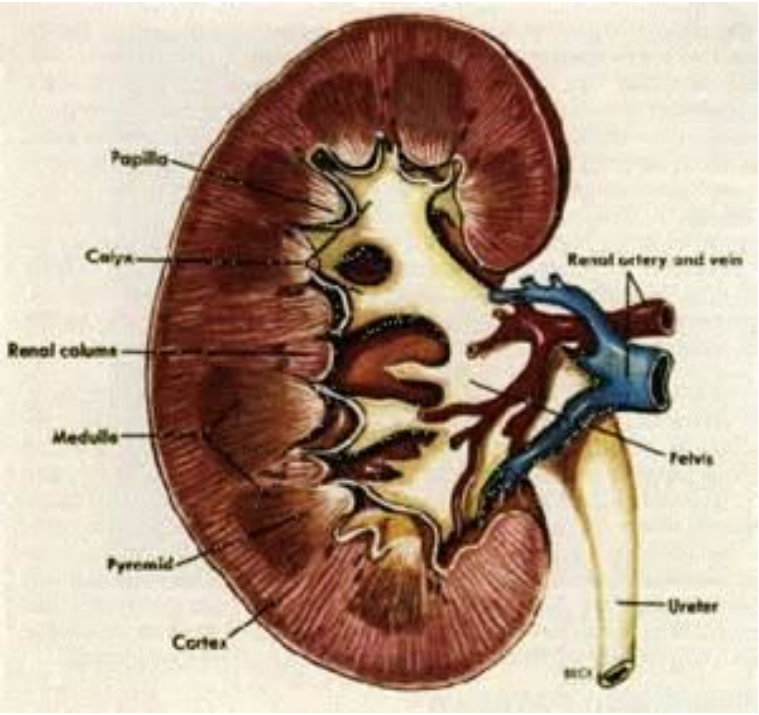

Fig 1: Gross anatomy of the kidney.

There are two kidneys in the human body. They are located in the retro peritoneal compartment on each side of the central vertebral column. Due to the presence of the liver in the right hypochondria the right kidney is placed slightly more caudally as compared to the left.

Medially the kidneys have the hilum where the renal vasculature and the ureter enter and exit the kidneys. More centrally there is an area containing predominantly fat and is called the renal sinus. Each kidney is surrounded by a fibrous capsule, a perirenal fat and a thin connective tissue layer which constitute the Gerota'sfascia (3).

The renal parenchyma is divided into the outer cortex and the inner medulla. The medulla is appear as cone shaped structures called the renal pyramids. The base of the pyramid faces the renal cortex while the tip called the renal papilla points towards the renal sinus.

ANATOMY OF THE NEPHRON

The nephrons are the functional units of the kidneys. There are approximately 1 million nephrons in each kidney at birth. The various parts of the nephron are the Bowman's capsule, glomerulus, proximal and distal tubulesand the loop of Henle (3).

The glomerulus constitutes a ball of capillaries which is surrounded by the Bowman's capsule. The Bowman's capsule is double walled structure which continues as the proximal tubule. The proximal tubule is located in the cortex (3).

The loop of Henle extends into the medulla and returns back into the renal cortex as the distal tubule. The distal tubule lies adjacent to the glomerulus and end as the collecting ducts. The collecting ducts converge into the minor calyx which is located in the renal papilla.

Multiple such minor calyces constitute a major calyx. There are ~ 2-3 such major calyx in each kidney. The major calyx converges into the renal pelvis. The renal pelvis is located within the renal sinus. The renal pelvis continues as the ureter which is narrower and leaves the kidney at its hilum. The urine from the kidney reaches the urinary bladder through the ureter (3,4).

ARTERIAL SUPPLY OF THE KIDNEY

The renal artery supplies oxygenated blood to the kidneys. The renal artery arises from the aorta as a direct branch and enters the kidney at its hilum. First the main renal artery divides into the segmental arteries and then the interlobar arteries (4).

These interlobar arteries traverse the renal columns and reach the renal cortex. These interlobar arteries further branch to form the arcuate arteries which supply the renal cortex. These arcuate arteries contrary to its name do not form any collaterals within the kidney. Hence the nephrons which are the functional unit of the kidney are supplied by end arteries(4).

VENOUS DRAINAGE OF THE KIDNEY

In the nephrons the inter lobular arteries branch out to form the afferent arterioles and enter the glomerulus. They exit out of the glomerulus as the efferent arterioles. The efferent arterioles branch out into a web of capillaries which surround the tubules. The vasa recta are formed by a subset of these capillaries which crawl along the loop of Henle into the medulla(3,4).

The venous drainage run parallel to the arterial supply as interlobular / arcuate /interlobar veins. These eventually form the main renal vein which exits the kidney through the hilum. The main renal vein eventually drains into the inferior vena cava (3,4).

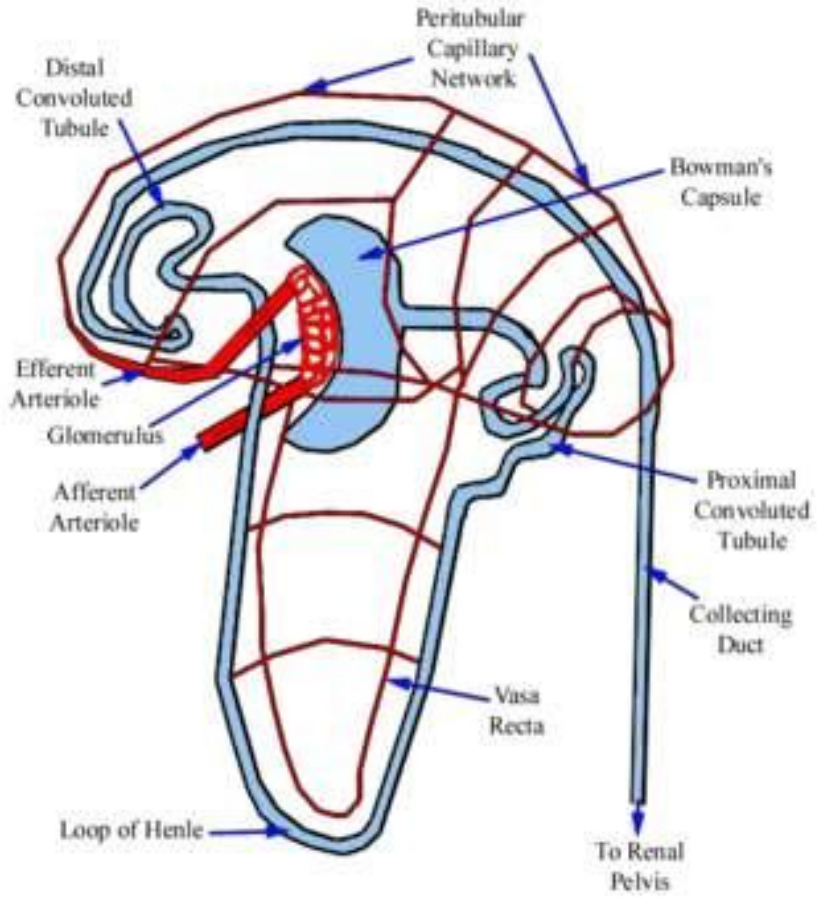

Fig 2: Line diagram of the nephron.

RENAL FUNCTION

The kidney has five main functions as described below in appropriate headings:

1) Excretion of waste
2) Water and electrolyte balance
3) Blood pressure regulation
4) Red blood cell regulation

5) Calcium regulation.

The kidney along with the liver plays a vital role in excreting waste products produced as an end result of various metabolic processes in the body.

The most grossly evident renal function is regulation of water balance in the body by formation of urine. This also relates to the electrolyte and the acid –base balance carried out by the kidneys (3,4,5).

In response to decrease in blood pressure the kidney secretes a hormone called renin. Renin in turn increases the formation of an active hormone called angiotensin 2. Angiotensin 2 is a potent vasoconstrictor and causes elevation of bloodpressure. It also causes increased secretion of aldosterone from the adrenal cortex which causes increased absorption of sodium from the renal tubules.

This in turn leads to production of antidiuretic hormone from the posterior pituitary resulting in increased reabsorption of water from the collecting system of the nephrons. Eventually there is increase in fluid volume and elevation of blood pressure (3,4,5).

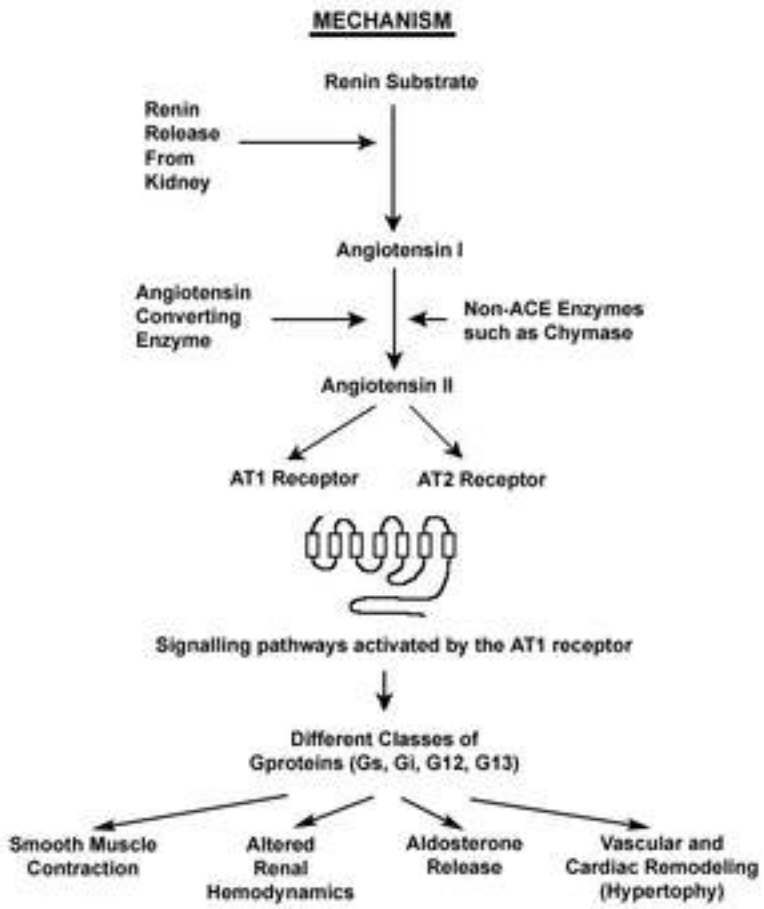

Fig 3: Flow chart of the renin angiotensin mechanism.

The kidney is also the source of erythropoietin. This stimulates the bone marrow to produce more red blood cells. The stimulus for production of erythropoietin is fall in blood oxygen saturation.

Vitamin D3 is formed in the skin as a result of exposure to the sun. This is converted into 25-hydroxycholecalciferol in the liver. 25-hydroxycholecalciferol formed in the liver is in turn converted into 1,25-dihydroxycholecalciferol in the kidneys.

When there is a fall in levels of extracellular calcium, the parathyroid gland secretes the parathyroid hormone which causes renal activation of Vitamin D (3,4,5).

This active form of Vitamin D causes increased intestinal and renal reabsorption of calcium / increased osteoclastic activity of the bones. Eventually these steps lead to increased extracellular levels of calcium.

URINE FORMATION

Three major steps are carried out by the kidney in the process of formation of urine. These three steps balance each other to match the excretion or retention of specific substances depending upon the need of the body. Each of these three steps is described briefly below.

1) Filtration
2) Reabsorption
3) Secretion

FILTRATION

This step of urine formation occurs in the renal corpuscle. From the glomerular capillaries to the Bowman's capsule fluid transportation occurs passively. The membrane across which this transportation occurs consists of fenestrated glomerular capillaries, basement membrane and podocyte cells. These podocyte cells constitute the visceral layer of Bowman's capsule (5).

This membrane functions by allowing water and small solutes to pass through it freely. However the membrane prevents larger solutes like proteins from being filtered. The filtration pressure is driven by the net gradient caused by differences in colloid osmotic and hydrostatic pressures. The value of this gradient is ~ 10 mm Hg (5).

The amount of filtration that occurs across the membranes depends on plasma flow and the filtration fraction. The proportion of cardiac output to the kidneys far outweighs the metabolic needs of the organ. Around 20% of the cardiac output or 1200 ml/min of blood enters the kidneys in a healthy male. Within the kidneys the cortex receives

around 90% of the renal blood flow. This high flow ensures large volume of filtrate and regulation of substances that needs to be excreted or retained. Around 180 L of filtrate or primary urine is produced every day (5).

REABSORPTION AND SECRETION

The primary urine filtered by the glomerulus now flows through the proximal tubule, Henle's loop, distal tubule and finally the collecting duct. Here the electrolytes and other organic substances are reabsorbed from the primary urine. Various methods like passive filtration and active reabsorption are involved in this process. Only 1% of the primary urine remains after the process of reabsorption in the collecting ducts (3,4,5).

RENAL FUNCTION ASSESSMENT

Various methods exist for assessing renal function. They are either direct or indirect measurements of the kidneys ability to clear metabolic waste. In order to assess and physically quantify the kidney's ability to clear waste products, the clearance of specific such substances can be derived. The amount of plasma that is completely cleared of a particular substance per minute is the plasma clearance value of that substance (6).

The mechanism of clearance of each substance varies and determines which of the above mentioned physiological process was involved. The glomerular filtration rate or GFR is the most important step as it is involved in all the excretory functions of the kidney. Hence measuring GFR to assess renal function is a vital step to evaluate renal pathology.

Originally assessment of renal function or clearance involved measurement of a substance produced endogenously called creatinine(6).

Creatinine is a substance formed in the body as a product of muscle degradation and is predominantly cleared by glomerular filtration and to a far lesser extent by tubular secretion. The creatinine clearance is calculated based on the clearance equation and approximation with Cockcroft-Gault or modification of diet in renal disease equations(7,8).

In day to day practice plasma creatinine level is extensively used as an indirect measure of renal clearance. But the limitation is that creatinine level depends on a multitude of

other parameters such as age, body weight, diet, physical activity etc. It is also insensitive in moderately decreased renal function.

Recently another endogenous substance called cystatin C was recommended for estimating GFR(9). Cystatin C was considered an advantageous alternative as it was independent of gender or muscle mass. Hence a higher accuracy was reported as compared to creatinine(10).

However the gold standard for GFR assessment is measuring the clearance of a substance called inulin which is an exogenous polysaccharide. Inulin is an ideal filtration agent to assess GFR as it has the properties of being freely filtered in the glomerulus but is not reabsorbed or secreted in the tubules. Besides inulin is neither produced nor metabolized in the kidneys. But the limitation is that inulin clearance test is expensive and time consuming.

The other relatively more convenient filtration markers are 51Cr-EDTA or iodinated contrast medium iohexol(11).

MEASUREMENT OF RELATIVE RENAL FUNCTION BY NUCLEAR MEDICINE

Calculation of glomerular filtration rate (GFR) is a very vital and integral part of comprehensive evaluation of renal pathology especially in the setting of renal donation. The various methods of assessing GFR described in the above section will give total GFR of both kidneys.

Their utility is limited especially when only split renal function and not total renal function is needed for clinical decision making as in the setting of renal donation.

Theoretically selective urine collection via ureteric catheters can calculate relative renal function but due to its invasiveness it is considered practically unacceptable.

In that background split renal function assessed by radionuclide methods, a non-invasive investigative modality is very useful and are routinely performed. In this method gamma cameras are used for visualization and quantification of radioactive tracer counts in each kidney. An ideal radioactive tracer for nuclear renal scan is one which has a high extraction fraction in the kidneys. This is very essential to obtain images with an ideal signal to noise ratio.

Technetium, 99m Tc is now the most commonly used isotope due to its ideal physical properties and high availability. 99mTc-DTPA is most commonly used in our institution for nuclear renal scans.

Various algorithms are available for processing raw data picked up by the gamma cameras. But the most widely applied method is that of Patlak-Rutland plot where a graphical model in specified time intervals based on unidirectional transport of a tracer from one compartment to the other. This particularly useful for assessing renal clearance(12).

In this method a plasma input curve, renal uptake curves of each kidney which are background corrected are derived and by applying the Patlak-Rutland plot relative renal function can be calculated(13).

COMPUTED TOMOGRAPHY (CT) IN VOLUNTARY KIDNEY DONORS.

It must be remembered that a living renal donor is actually one of the very few subjects in the healthcare network that cannot be called patients and are actually healthy volunteers. As with any medical or surgical intervention there must be a careful analysis of the risk versus benefit ratio. However for a living renal donor there are no direct personal benefits but the risks and

inconveniences of a surgical procedure are very much there. Therefore itis important to ensure that the donor does not suffer harm as a result of donation.

In current day practice CT scan is done preoperatively for a potential living donor for anatomic assessment prior to transplantation. It has been well established that CT is very essential for preoperative planning as it gives excellent anatomical detail of the urinary tract and the blood vessels(14-17).

The other important aspect of preoperative planning is the determination of the split renal function or the relative renal function. Relative renal function of a kidney is actually the contribution of that kidney in percentage to the total renal function. There are various methods of determining relative renal function as described earlier under the heading of renal functional assessment.

However currently in the setting of in a voluntary kidney donor prior to donation functional assessment of the kidneys is done by nuclear scintigraphy. The purpose of assessing relative renal function is to see if the potential renal donor is fit for donation and if so which kidney is to be donated. In the process of renal donation the donor must not suffer any harm. Hence only

the kidney contributing lesser to the total renal function or with lower relative renal function can be donated. In other words the functionally dominant kidney stays with the donor.

This study aims to determine relative renal function from contrast enhanced CT and compare the results with that of Tc99m DTPA scintigraphy. In the scenario of voluntary renal donation only relative and not absolute renal function is required for clinical decision making.

Literature review on various CT methods to determine differential renal function and assess correlation with reference nuclear scintigraphy showed a mixed correlation coefficient ranging from as low as 0.4 to as high as 0.9(18–29).

Hence there is uncertainty regarding whether CT based methods of relative renal function determination can replace nuclear renography. Recent studies by Soga et al analyzed various CT methods for assessing differential renal function and found few methods were superior to others(30).

The aim of this study is to estimate split renal function using CT methods that had a high correlation coefficient in Soga's study. By doing so we can assessreproducibility of results shown by Soga et al and determine if CT can replace Tc99m DTPA scintigraphy in renal

functional assessment before renal transplantation and if so which of the CT methods is most useful in our setting.

Soga et al found that four CT methods of calculating relative renal function had high correlation coefficients ranging from 0.79-0.84. The methods are as follows:

1) Semi-automated volume method
2) Attenuation capacity method
3) Modified ellipsoid method
4) Parenchymal area method.

METHOD 1: SEMI-AUTOMATED RENAL VOLUME:

Renal volumes derived by various CT methods correlate well with renal function also permits concurrent determination of split renal function(18–28). As it is important to leave the better functioning kidney with the donor it is also important to prevent nephron under dosing of the transplanted kidney as it can lead to poor allograft function.

Saxena and his teamhad performed a retrospective analysis of 54 patients with the aim to determine and establish the relationship between donor kidney volumes and post-transplant renal graft function. The 54 patients enrolled in this study were renal transplantation recipients. All these patients had undergone magnetic resonance imaging (MRI) as a part of preoperative evaluation.

The renal volumes were calculated by MRI and compared with post transplantation graft function. Along with transplant kidney volume the recipient body weight was also assessed. The ratio between transplant kidney volume and recipient body weight was determined separately for each donor-recipient pair. These ratios were called the nephron-dose ratio.

Based on this nephron dose ratio they were further divided into 3 groups. Those with a ratio greater than 2.7 were placed in the high group whereas those with ratios between 2-2.7 and less than 2 were placed in the moderate and low groups respectively.

Glomerular filtration rate (GFR) was assessed for each transplant kidney at six and twelve months and compared with the nephron dose ratios. It was found that GFR correlated well with transplant kidney volume and recipient body weight ratio at 6 and 12 months (r=0.46; P=0.0005 and r=0.41; P=0.003). Hence they concluded that donor renal volumes calculated preoperatively can be useful to predict recipients at risk for a low GFR post transplantation(18).

Moorthy and his colleagues performed a critical appraisal of measurement of renal dimensions in vivo. They found that contiguous computed tomography(CT) sections to evaluate renal

volumes were reliable, objective and easily reproducible in assessing renal volumes. They also concluded in their critical appraisal that ultrasound (US) because of its inherent intra and inter observer variability made it a non-reliable modality to assess renal volume(31).

Morrisroe and his team performed a study to see if CT can be used to determining renal function. They proposed to measure renal volumes by CT scan and used percent renal volume of each kidney as surrogate marker for differential or split renal function. A total of 33 patients with chronic obstruction due to varied causes were included in their study and underwent CT scan and diuretic enhanced nuclear scintigraphy.

Of these 33 patients who underwent CT, 23 of them had a contrast enhanced CT whereas 10 had only a non-contrast CT. CT images were retrieved and displayed on a research work station where they were reviewed.

The authors proposed a method called semi-automated boundary delineation with manual editing. Here the researcher would manually draw a line along the renal contour. The contour drawn would then be carefully edited to exclude non-parenchymal parts of the kidney such as the collecting system, vessels, calcification, cysts etc...

This was done for each slice of the CT scan which contained the kidneys. Once this was done the workstation would automatically give the parenchymal area within the contour. Total volume of each kidney was then computed by summing the products of area measurements

and slice thickness. Finally by dividing right and left renal volumes by combined right and left renal volumes would give right and left percent renal volumes.

The percent renal volume for each kidney was then compared with percent renal function calculated from the nuclear renal scan. The authors observed a strong correlation between percent renal function and percent renal volume in all cases (r 0.90, p0.001).

The authors thus concluded that differential renal volumes calculated by semi-automated method had a high correlation with split renal function calculated by nuclear renal scan(27).

A prospective study was done by Sarma and his colleagues on 21 patients with unilateral obstructive uropathy. Their aim was to study the correlation between renal parenchymal volumes calculated by CT and split renal function calculated by 99mTc-DTPA renal scan. The CT scan was done in a 64 slice helical CT which estimated renal volume depending on the reconstruction of arterial phase images and volume rendering techniques. Percent renal volumes were obtained by CT and then were compared with split renal function values assessed by99mTc-DTPA renal scan using Pearson's coefficient.

A strong correlation was observed between relative renal volumes were by CT and split renal function values assessed by 99mTc-DTPA renal scan (r -0.828) in obstructed and (r 0.827) in non-obstructed renal units with a $p < 0.001$. Hence the authors concluded that there was a strong correlation between relative renal volumes assessed by CT and split renal function by 99mTc-DTPA renal scan(32).

Soga and his team employed the semi-automated method of renal volume calculation by CT and compared it with nuclear renography as the reference standard. Here the researcher would manually draw a line along the renal contour. The contour drawn would then be carefully edited to exclude non-parenchymal parts of the kidney such as the collecting system, vessels, calcification, cysts etc... This was done for each slice of the CT scan which contained the kidneys.

Another radiologist unaware of the study data would carefully review and correct the segmentations. Once this was done the workstation using commercial softwarewould automatically give the parenchymal volume within the contour.Hence volume of both kidneys within the region of interest was obtained separately.

The relative volume of each kidney will then be calculated as renal volume divided by the total renal volume of both kidney. This was compared with the results of nuclear renal scintigraphy which showed a high correlation coefficient of 0.83 with a $p < 0.001$.

Hence the authors concluded that semi-automated method of relative renal volume calculation correlated well with split renal function calculated by nuclear renal scan(30).

METHOD 2: ATTENUATION CAPACITY

Glomerular filtration can be determined by measuring the clearance of a particular substance which is known to be filtered in the glomerulus. A substance which is freely filtered through the glomerulus, not bound to plasma proteins, which is not secreted / metabolized / absorbed in the tubules and is physiologically inert is considered an ideal GFR agent. Inulin, 99m Tc –DTPA and labeled contrast media are a few markers or agents used to determine GFR(28).

Recently iohexol which is a non-labeled contrast medium has been increasingly used as a reliable GFR agent to determine the concentration of iohexol in plasma and urine(20–25,33).

Incidentally iohexol is also the intravenous contrast agent that is commonly used for contrast enhanced CT scan.The amount of marker that has accumulated in the kidney within two minutes of intravenous contrast agent (iohexol) injection and before any of the injected contrast has left the kidney via the collecting system is considered to be directly proportional to the GFR of that kidney(28).

Hence there is a possibility that relative GFR can be derived from CT scans using iohexol as contrast medium.

Frennby and his colleagues based on the above mentioned principle looked at whether split renal function determined by CT scans using iohexol as contrast medium correlated well with relative renal function determined by reference 99mTc-DTPA renal scan.

In that study the authors found an excellent correlation(r 0.98) between split renal function assessed by CT scan using iohexol as contrast media and that determined by 99mTc-DTPA renal scan. Hence it can be safely concluded that the amount of contrast media that accumulates in the renal parenchyma a few minutes after intravenous bolus injection but before any of it has left the kidney via the collecting system is directly proportional to the GFR of that kidney.

When CT scan employs intravenous contrast agent it can also be inferred that GFR is directly proportional to the attenuation capacity of contrast agent in that kidney. Hence larger the volume of a kidney and larger the mean attenuation capacity of contrast in that kidney, larger will be the GFR of that kidney(33).

Based on the assumption that accumulation of contrast medium is directly proportional to the renal function Nilsson and his colleagues compared spilt renal function calculated by CT with relative renal function calculated by renal nuclear scintigraphy.

They retrospectively analyzed CT images and renograms of 27 potential renal donors. They measured area and mean attenuation of the kidneys by drawing manual region of interest around the kidneys with the aim of including normal renal functional parenchyma and excluding nonfunctional areas such as cyst, calcification, fat etc...

The mean attenuation value in HU and the area of the region of interest(ROI) were noted and the area under the ROI was multiplied by slice thickness which was around 0.8 cm to determine renal volume under ROI in that slice.

The total kidney volume was then obtained by adding the volumes of all slices. To determine the total attenuation capacity of each kidney the volume of each slice was multiplied by mean attenuation of that slice and the products of all the slices of each kidney were added. The results showed a moderate correlation between CT and nuclear renal scan methods of determining relative renal function.

The correlation coefficients were around 0.43 but the range of results was narrow. The ratio between the two kidneys was even more with CT than with renogram (CT – 50 +/- 2.1% ;Renogram – 48 +/-2.9%).

They also determined that the mean difference between the two methods was 3 +/-2.3%. They concluded saying that CT can replace renograms for functional assessment of potential renal donors(28).

Tarek and his team performed a study on 80 consecutive renal donors to assess if contrast enhanced spiral CT can be used to predict renal function. Functional assessment of each kidney was done by data collected from the nephrographic phase images of the kidneys. For quantitative assessment ROIs were drawn over the renal parenchyma of each kidney carefully excluding any cyst, fat or calcification in the parenchyma.

Once this was done another ROI of the supra renal aorta was drawn. Based on the principal of Frennby as described earlier mean attenuation value of each kidney was calculated. The total MAV of each kidney was divided by the MAV of the suprarenal aorta using the concept of Miles(34). The value obtained by dividing MAV of each kidney over the MAV of the aorta was called the uncorrected CT clearance of that kidney. It was found that in all renal donors in that study the ratio between uncorrected CT GFR and radioisotopic GFR was 1:5.

Hence corrected GFR of each kidney was calculated by multiplying uncorrected CT GFR of each kidney by 5.

The results derived by this method were compared with GFR measured by 99mTc-mercaptoacetyltriglycine.

They found a correlation of $r=0.54$, $p<0.001$ between the GFR calculated by both methods. They also found that the mean isotope clearance of the right and left kidneys were not significantly different from that of mean CT clearance. They also recommended spiral CT with contrast as a single modality for preoperative evaluation of renal donors(35).

Summerlin and his colleagues retrospectively 173 renal donors by CT and radionuclide renogram based measures of split renal function. The CT based method of calculating relative renal function involved semi-automatic creation of 3D models from pre contrast, arterial and excretory phase images. Measurements of CT renal volumes and attenuations were derived from these 3D models of the kidneys.

The mean renal attenuation and volume were used in calculating net accumulation of contrast and eventually split renal function. Split renal function from CT were calculated from arterial and excretory phases as well as based on split renal volumes.

The results revealed no significant difference from radionuclide renogram ($p>0.05$, t test). Pearson correlation values had a range of 0.36 to 0.63 for various methods. The excretory and renal volume methods had the narrowest range and demonstrated a linear and a non-zero relationship to the renogram values. Bland-Altman analysis confirmed majority of difference between each CT method fell within 95% CI of the differences(24).

As described earlier Soga and his team used semi-automated ROIs to assess renal volumes as in method 1. The attenuation value of the kidney was alsodetermined by drawing region of interest around the renal contour in each slice as in method 1; mean attenuation value of kidney wasdisplayed automatically after the entire ROI is drawn. The venous phase corresponds

to the nephrographic phase of the kidney and is chosen to determine the attenuation capacity of the kidney.

Attenuation capacity was then calculated by multiplying the volume derived by method 1 with the mean attenuation value of each kidney.The relative attenuation capacity of each kidney was obtained dividing attenuation capacity of one kidney by the sum of attenuation capacity of both kidneys.This value was compared with the split renal function assessed by nuclear renal scan. The results showed a correlation coefficient of 0.79 $p< 0.001$. Hence this was one of the CT methods which had a good correlation of split renal functions with nuclear renal scans(30).

METHOD 3: MODIFIED ELLIPSOID VOLUME

Renal volumes derived by various CT methods correlate well with renal function(18–23). This also permits concurrent evaluation of split or differential or relative renal function(24–28). Renal dimensions can be easily assessed on CT due to the excellent anatomical detail they provide.

Logically it would be thought that the combination of CT attenuation value pre and post contrast and morphological parameters would estimate renal function better than morphology

alone as it inherently includes parameters such as perfusion and plasma clearance of iodinated contrast. This in fact has been considered as reliable as the gold standard of inulin clearance for estimating renal function(27).

But growing literature evidence suggest that renal morphology such as volume and area alone are sufficient for estimating relative renal function in the setting of voluntary kidney donation(20,23–25). Similar studies have been done on patients with chronic kidney disease and renal artery stenosis which shows good correlation between CT volumes based estimation of split renal function and renal scintigraphy(28–30).

Various studies in the past have attempted to calculate ellipsoid volume of the kidney by different modalities such as ultrasound, computed tomography or magnetic resonance imaging. A study was done by Bakker and his colleagues on 20 volunteers in 1998 to assess the accuracy and reproducibility of Ultrasound with ellipsoid volume method in calculating renal volume. The ellipsoid volumes calculated by ultrasound were compared with renal volumes determined with voxel count method on magnetic resonance imaging.

The latter method was considered the reference standard. Two independent observers performed the measurements twice to assess repeatability. The study concluded with the impression that application of ellipsoid formulae method to determine renal volumes based on US were neither accurate nor reproducible(36).

In an another study done by Bakker and his team they found underestimation of renal volumes calculated by ultrasound and magnetic resonance imaging using the ellipsoid formula method(30,37–39).

Attempts were made by various investigators to determine renal volumes by on computerized tomography. One such large study which used ellipsoid method of renal volume estimation was done by Sorbellini and his team on 1018 patients. These patients had undergone radical or partial nephrectomy. The estimated renal volumes were incorporated into a prognostic normogram for postoperative renal insufficiency.

The normogram predicted 7 year probability of renal failure with a correlation coefficient of 0.84 but did not specifically determine the accuracy of renal volume estimates by ellipsoid method(37).

In 2011 Hwang and his team looked at various CT methods to determine renal volume in 138 voluntary kidney donors. The reference standard was volume calculated using kidney measurements using calipers following nephrectomy. They concluded that renal volumes estimated by modified ellipsoid formula method on CT had a high correlation coefficient of 0.72(40).

More recently in a study done by Soga and his team in 2012 on 38 potential voluntary renal donors, the modified ellipsoid method to assess the renal volumes from CT measurements were performed. Nuclear renography was considered the reference standard. The modified ellipsoid method of renal volume estimation had a high correlation coefficient of 0.84 with renal scintigraphy. They also concluded that this method of renal volume estimation had the highest accuracy and consumed the least time for post processing(30).

Though earlier studies with US and MRI using this method reported poor accuracy, this study showed excellent correlation. The authors also pointed out a few factors that could explain the promising results by modified ellipsoid method on CT. First this study looked at potential kidney donors were only relative renal function and not absolute renal function was important for clinical decision making.

Hence the systematic underestimation of renal volumes would not negatively impact results in that scenario. Next the measurements obtained by MRI were not done so along the true axes of each kidney. Data acquired in true axial, coronal and sagittal planes are subject to geometric errors. Finally ultrasound measurements are prone to poor inter observer agreement especially in the setting of a poor echo window(30).

The ellipsoid volume is defined as length x breadth x thickness x (Pi/6). These measurements will be obtained from sagittal and coronal maximum intensity projections. Length and width would be derived from coronal images whereas thickness is measured from the sagittal plane.

Kang and his team made a comparative study of various CT methods for assessing renal length in renal transplant donors. The sizes of the kidneys (length, width and thickness) were measured after donor nephrectomy using sterilized vernier calipers and taking care to exclude as much peri-renal fat as possible. They concluded that abdominal coronal CT sections predicted renal lengths most accurately (41).

Oblique MIP images will be obtained to maximize the renal length, breath and thickness. Width and thickness will be measured at the level of the renal hilum.The relative modified ellipsoid volume of each kidney will be obtained by dividing volume of each kidney with the sum of volumes of both kidneys(41).

METHOD 4: PARENCHYMA AREA

It is well known fact that diseased kidneys undergo a degree of parenchymal atrophy with time.This could be secondary to varied causes like diabetes, pyelonephritis, obstruction, glomerulonephritis etc... It is also known well that greater the atrophy greater is the reduction in renal parenchymal volume. It is also known that renal volumes derived by various CT methods correlate well with renal function(18-23). This also permits concurrent evaluation of

split or differential or relative renal function(24-28). Renal dimensions can be easily assessed on CT due to the excellent anatomical detail they provide.

Kaplon and his colleagues performed a study on 28 patients with unilateral renal obstruction who had undergone CT scan and nuclear renography. Their aim was to determine the relationship between renal parenchymal thicknesses on CT and relative renal function on nuclear renography in chronically obstructed kidneys.

Linear regression analysis comparing renogram split renal function to renal parenchymal thickness ratio revealed a correlation coefficient of 0.48 ($p<0.001$). They concluded that renal parenchymal thickness on CT was a powerful predictor of relative renal function in obstructed kidneys(42).

Federet all evaluated correlation between measured renal parenchymal area and relative renal function calculated by renal scintigraphy. A total of 111 patients who underwent CT scan and renal scintigraphy were included in this study(43).

The average parenchymal thickness for each kidney was defined as the mean of six thickness values. Of these 6 values three were taken at the upper pole and three at the lower pole.These values were taken from axial images in the cut where the collecting system would have just started to appear. Three measurements will be taken from each pole by drawing lines from the

margins of the collecting system to the adjacent cortical margins. Hence a total of six values were obtained for each kidney separately. When the sum of all six values were calculated and divided by six, it would give the average parenchymal thickness for that kidney.

The parenchymal area is defined as the product of average parenchymal thickness and renal length.The relative parenchymal area of each kidney was obtained bydividing parenchymal area of each kidney with the sum of parenchymal area of both kidneys(42).

They found an excellent correlation between relative renal function calculated on CT by parenchymal method and that from renal scintigraphy. A Pearson's coefficient of 0.959 with an average difference of 4.73% was observed between predicted and observed relative renal function. They also compared a group of 22 patients with positive urine culture to 89 others with negative urine cultures and determined an average functional difference of 6.54% to 4.28% with Pearson's correlation of 0.955 in the culture positive group to 0.965 in the culture negative group. The results of 89 patients in the culture negative group were further compared based on contrast vs. non contrast CT and obstructed vs. unobstructed kidneys. No statistical difference was noted with contrast administration.

However on comparing obstructed and unobstructed kidneys they found a statistically significant difference in favor of unobstructed kidneys showing a Pearson's correlation of 0.743 in the obstructed to 0.975 in the unobstructed group with a functional difference of 3.28% to 5.10%. Hence they concluded that renal parenchymal area calculated by this method on CT scans correlates strongly with relative renal function derived from renal scintigraphy.

In another study done by Soga et all on 38 patients, they employed the above mentioned parenchymal area method as one of the CT based methods for determining relative renal function. That study showed a correlation coefficient of 0.79 comparing split renal function on CT by this method to nuclear renography(30)..

MATERIALS AND METHODOLOGY

STUDY DESIGN:

This is a Prospective study to assess diagnostic accuracy.

STUDY TYPE:

Analytical

SETTING:

Christian Medical College is a tertiary center hospital located in the town of Vellore in Tamil Nadu. This is now a 2800 bedded hospital which was established in the year 1900. The annual outpatient visits are about 2 million with inpatient admissions of upto 120,000. The institution also has multiple specialtyand super specialty units with the Departments of Radiology, urology, nephrology and nuclear medicine among them. The Radiology department was established in 1936 and now possesses a Picture

Archival and Communication system (PACS). There are approximately 80 radiologists working in this department.

SUBJECTS:

The study patients were potential voluntary kidney donors who attended the Nephrology Out Patient Clinics of Christian Medical College and Hospital for a potential renal donation.

INCLUSION CRITERIA:

1. All consecutive voluntary kidney donors who attended the Nephrology out Patient Clinics of Christian Medical College from December 2012 to October 2013.
2. Those of the above who underwent contrast enhanced computed tomography as a part of preoperative workup in Department of Radiology in our institution.
3. Those of the above who underwent nuclear scintigraphy as a part of preoperative workup in Department of Nuclear Medicine in our institution.

EXCLUSION CRITERIA:

All potential voluntary kidney donors selected by clinical and laboratory criteria who had,

1. Contraindications to computed tomography (CT) imaging.

2. Contraindications to use of non-iodinated intra venous contrast agent.

3. Presence of renal masses, multiple renal calculi or large polar cysts.

4. Presence of obstructive uropathy.

5. Contraindications to renal scintigraphy.

INFORMED CONSENT:

The Institutional Review Board waived the need for informed consent as there was no change in the existing CT protocol for the sake of this study and measurements obtained for the sake this study would not in any way influence the patient management or delay procedures.

SAMPLING:

The prospective study patients were referred to us from the nephrology OPD. All consecutive subjects fulfilling the inclusion criteria were enrolled in the study to avoid bias and no other specific sampling strategy was employed.

The selections of subjects were independent of the results of the reference standard (renal scintigraphy).

Baseline data of these subjects were entered in a structures profoma (Appendix 1).

TIMING:

The index tests (CT) was performed within one week of performing the reference standard test (renal scintigraphy). It was unlikely that the target health condition would change in the interim period between the two tests.

COMPUTED TOMOGRAPHY (CT) IMAGING METHODS:

CT scanner:

The study was performed in our institution in a Siemens Syngo (Somatom Emotion) machine which is a 16 slice multi detector CT.

PATIENT PREPARATION:

Standard precautions as for any patient undergoing contrast enhanced CT study was followed.

The patient was requested to be fasting for at least four hours before the scheduled timing for the scan. The patient's serum creatinine value waschecked before the study and had to be less than 1.4 mg%. The patient was asked about history of allergy and asthma in which case they wouldadvised to

take Tablet. Prednisolone 30 mg, twelve and two hours before the procedure along with an oral anti histamine.

In case of previous severe contrast reactions or pregnancy there was discussion with the referring clinical colleagues regarding further plan of action.

CT PROTOCOL:

- Topography

- CT scans were performed with 120 effective mAs and 130 Kv with a slice thickness of 5mm.

- CT scan images were initially obtained without giving intra venous contrast from the dome of the diaphragms to the symphysis pubis.

- CT renal angiography (diaphragmatic domes to aortic bifurcation) was done using 120 ml of intra venous non-iodinated contrast media at a rate of 4ml per second using a pressure injector. A trigger was placed in the descending thoracic aorta. The scan was started when 40 ml of contrast had reached the aorta.

- Nephrographic phase or the venous phase imaging was done from the dome of the diaphragm to the pubic symphysis. This scan was started after a delay of 60-75 seconds.

- After twenty minutes a delayed plain radiograph of the kidney, ureter and bladder was taken.

- Finally coronal and sagittal multiplanar reformats of the kidneys were reconstructed.

The intra venous contrast medium that was used in the study was Iohexol. The dose of contrast medium and the timing of imaging was constant for all participants.

SEQUENCES AND METHODOLOGY:

Relative function of each kidney was determined by each of the four methods described in earlier in the bibliography section. Mean attenuation capacity of the kidney; renal volume; renal length, width and thickness from multi planar reconstructions, parenchymal area estimation was performed by a single observer on Siemens workstation.

In addition the time taken for each CT method per patient was noted.The imaging results was viewed and interpreted by the principal investigator with the help of a co-investigator with experience in abdominal imaging. The observers were blinded to patient's clinical data and renal scintigraphy reports. The data was recorded on the proforma (Appendix 1).

METHOD 1: SEMI-AUTOMATED RENAL VOLUME:

In this method manual region of interest was drawn around the kidney in such a way to include normal renal parenchyma and exclude non- functioning areas like renal sinus fat, pelvis, calcifications and cysts. Using commercial software volume within the region of interest was derived. Hence volume of both kidneys within the region of interest was obtained separately.The relative volume of each kidney was then be calculated as renal volume divided by the total renal volume of both kidneys.

Fig 4: Method 1- Intra venous contrast enhanced CT axial sections of the abdomen at the level of the kidneys demonstrating manually corrected region of interest drawn on the right kidney as in Relative renal volume method. Note that the ROI includes normal enhancing renal parenchyma and excludes hilar fat and blood vessels.

METHOD 2: ATTENUATION CAPACITY

First semi-automated volumes of the kidneys were derived as in method 1. The attenuation value of the kidney was determined by drawing region of interest around the renal contour in each slice as in method 1; mean attenuation value of kidney is displayed automatically after the entire ROI is drawn. The venous phase corresponds to the nephrographic phase of the kidney and is chosen to determine the attenuation capacity of the kidney. Attenuation capacity was then be calculated by multiplying the volume derived by method 1 with the mean attenuation value of each kidney.The relative attenuation capacity of each kidney was obtained dividing attenuation capacity of one kidney by the sum of attenuation capacity of both kidneys.

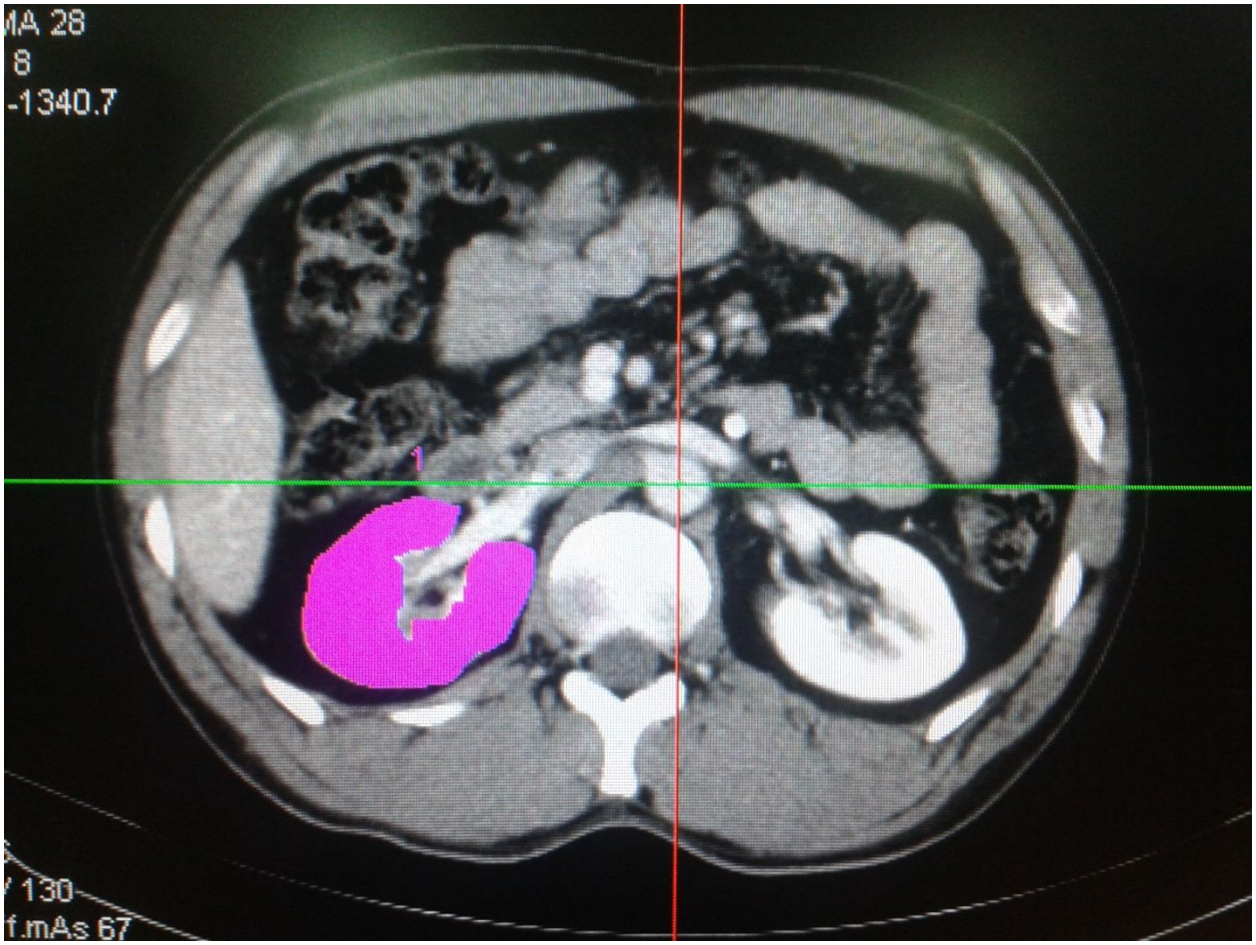

Fig 5: Method 2 - Intra venous contrast enhanced CT axial sections of the abdomen at the level of the kidneys demonstrating manually corrected region of interest drawn on the right kidney as in Relative Mean Attenuation Capacity Method. Note that the color shaded area includes normal enhancing renal parenchyma and excludes hilar fat and blood vessels.

METHOD 3: MODIFIED ELLIPSOID VOLUME

The ellipsoid volume is defined as length x breadth x thickness x (Pi/6). These measurements were obtained from sagittal and coronal maximum intensity projections. Length and width was derived from coronal images whereas thickness was measured from the sagittal plane. Measurements used 3 cm maximum intensity projections oriented along the true long axis of each kidney. Oblique MIP images were obtained to maximize the renal length, breath and thickness. Width and thickness were measured at the level of the renal hilum.The relative modified ellipsoid volume of each kidney wasobtained by dividing volume of each kidney with the sum of volumes of both kidneys.

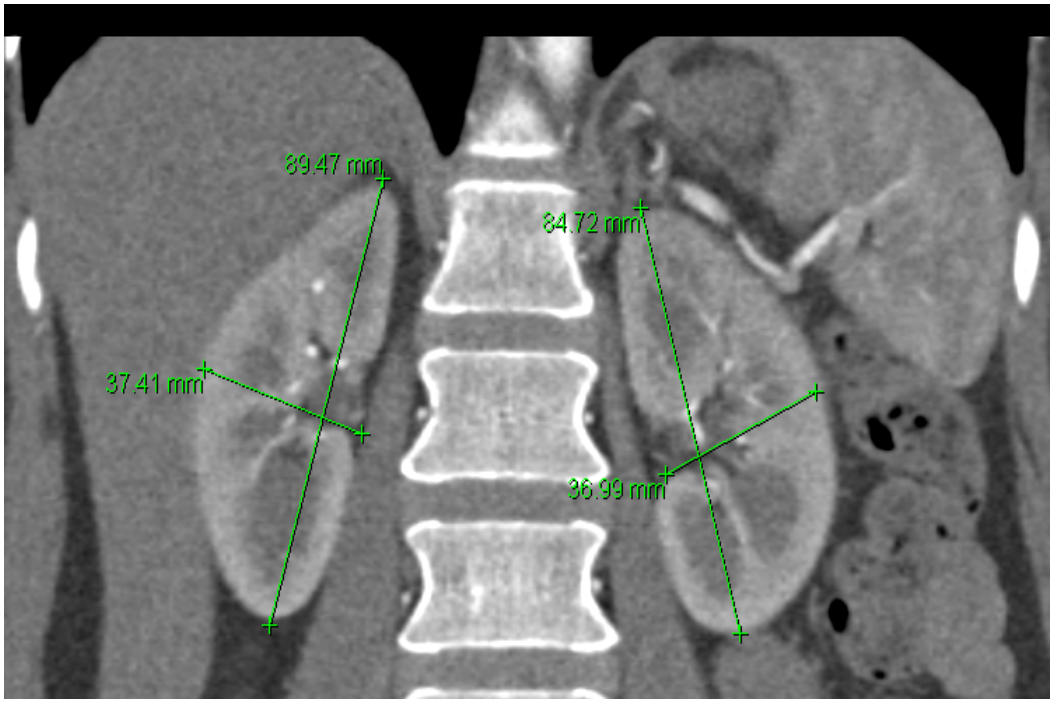

Fig 6: Method 3 –Multi planar coronal reformatted images of both the kidneys shows measurement of length and breadth of both the kidneys as in Relative Modified Ellipsoid Volume Method.

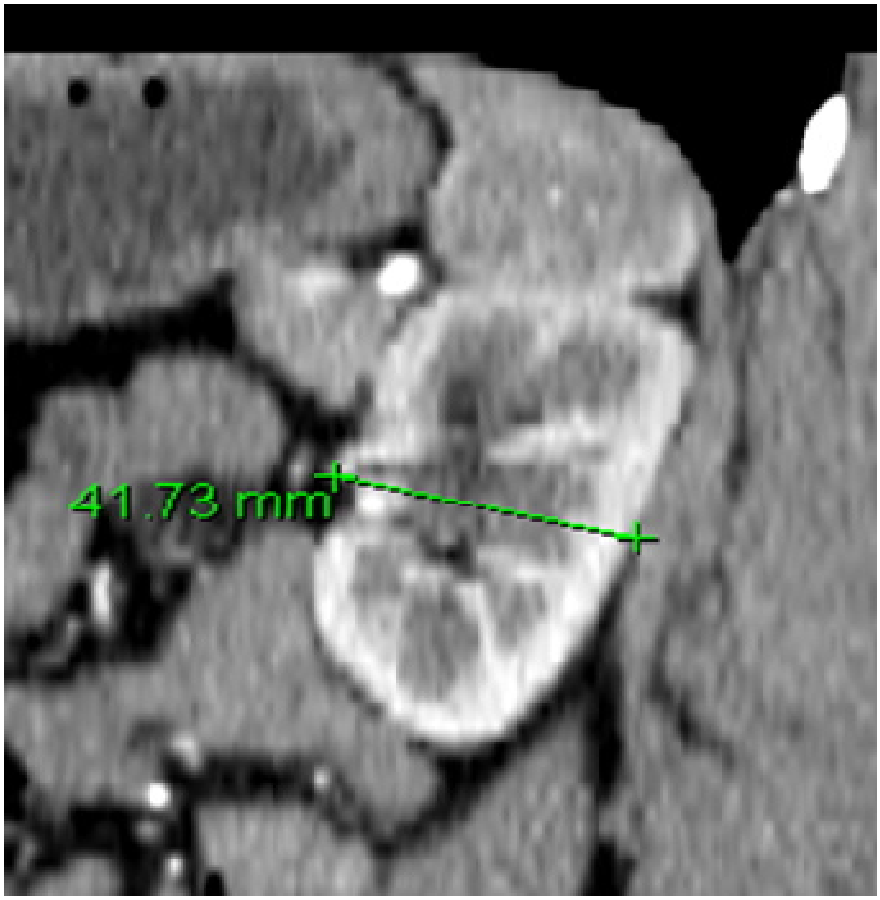

Fig 7: Method 3 – Multi planar sagittal reformatted images of the kidney shows measurement of thickness as in Relative Modified Ellipsoid Volume Method. Note that the measurement is taken by drawing a line through the renal hilum.

METHOD 4: PARENCHYMA AREA

The average parenchymal thickness for each kidney was defined as the mean of six thickness values. Of these 6 values three were taken at the upper pole and three at the lower pole.These values were taken from axial images in the cut where the collecting system had just started to appear. Three measurements were taken from each pole by drawing lines from the margins of the collecting system to the adjacent cortical margins. The renal length was measured as in method 3.The parenchymal area is defined as the product of average parenchymal thickness and renal length.The relative parenchymal area of each kidney was obtained dividing parenchymal area of each kidney with the sum of parenchymal area of both kidneys.

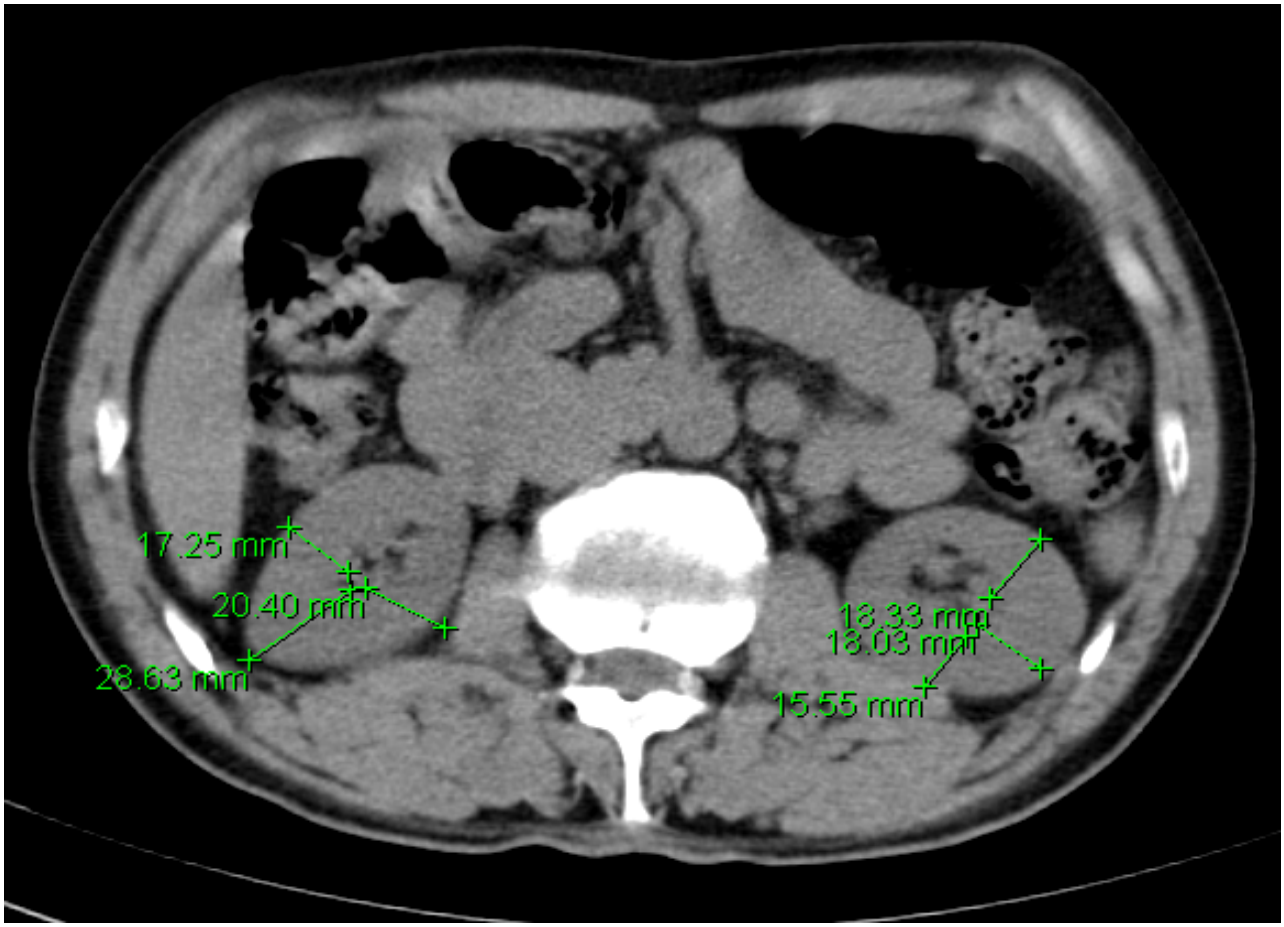

Fig 8: Method 4 – Axial pre contrast CT sections of the abdomen at the level of lower pole of both the kidney where the collecting systems have just appeared, shows measurement of three values (anterior-inferior, posterior-inferior and inferior-lateral) of both the kidneys as in Relative Mean Parenchymal Area Method.

Determination of split renal function by nuclear scintigraphy:

The reference standard is Tc99m DTPA renal scintigraphy which is done in the department of nuclear medicine in our institution. According to the current protocol for pre-operative evaluation of all potential voluntary kidney donors in these patients undergo a multi- phasecontrast enhanced CT for detailed anatomical evaluation and Tc99m DTPA renal scintigraphy for functional assessment (relative function of each kidney). The studies are reviewed and reported by two experienced doctors in the Department of Nuclear Medicine.

The relative renal function and DTPA clearance of each kidney was evaluated according to the method of Gates et al. (44, 45)

The following steps were followed:

Technique:

The patient was advised optimal hydration with two liters of fluid which was started a couple of hours before the procedure.From the patient's body weight and height the patient's body surface area and mid plane depth of the kidneys are calculated by using the formulae of George and Tonnesen respectively (46, 47). The mid plane depth of the kidneys can also be determined by ultrasonography or computed tomographic measurements.

The determination of glomerular filtration rate begins with determination of one minute pre-injection syringe count. This value is determined by stirring the count data in 128 x 128 matrixes by placing the radionuclide filled syringe 30 cm from the center of the collimator. After this step the patient is promptly positioned in front of the gamma camera and a bolus of intravenous 99m technetium

diethyelenetetraminepentaacetic acid(99m Tc DTPA) is given within 1-3 minutes. The usual bolus dose is around 111MBq.

The patient lies supine and the posterior view counts are studied. Acquisition of counts data begins from the time of intravenous bolus injection at the rate of 2 seconds per frame for one minute and fifteen seconds per frame for nineteen minutes thereafter.

After the intravenous bolus of radionuclide is given a one minute post injection syringe count was determined in the same way as the pre injection syringe counts were determined. From the pre and post injection syringe counts the value of net activity can be derived by subtracting the two values.

By adding all eight frames which were acquired at the rate of fifteen seconds per frame for two minutes composite images are acquired. Approximately 50% of the total background count is subtracted to optimize renal identification and is called background correction. This is achieved by drawing region of interests around both the kidneys to assess gross renal counts and semilunar areas of region of interest below both kidneys to assess background counts.

Subsequent step involves the subtraction of background counts from gross renal counts. This gives the net renal activity value which in turn implies the renal activity in both kidneys approximately 2-3 minutes following tracer injection.

After the step of background correction the values are depth corrected using Tonnesen formula (46). Once depth corrected these values (total renal counts) were then further divided by the net administered syringe counts. This in turn gives the percentage of tracer in each kidney within 2-3 minutes of tracer injection which is also the glomerular filtration rate of each kidney for that tracer. On

multiplying this value to the ratio of standard body surface area to body area the value of normalized GFR is computed.

Finally the total GFR, percentage and relative contribution from both the kidneys are derived.

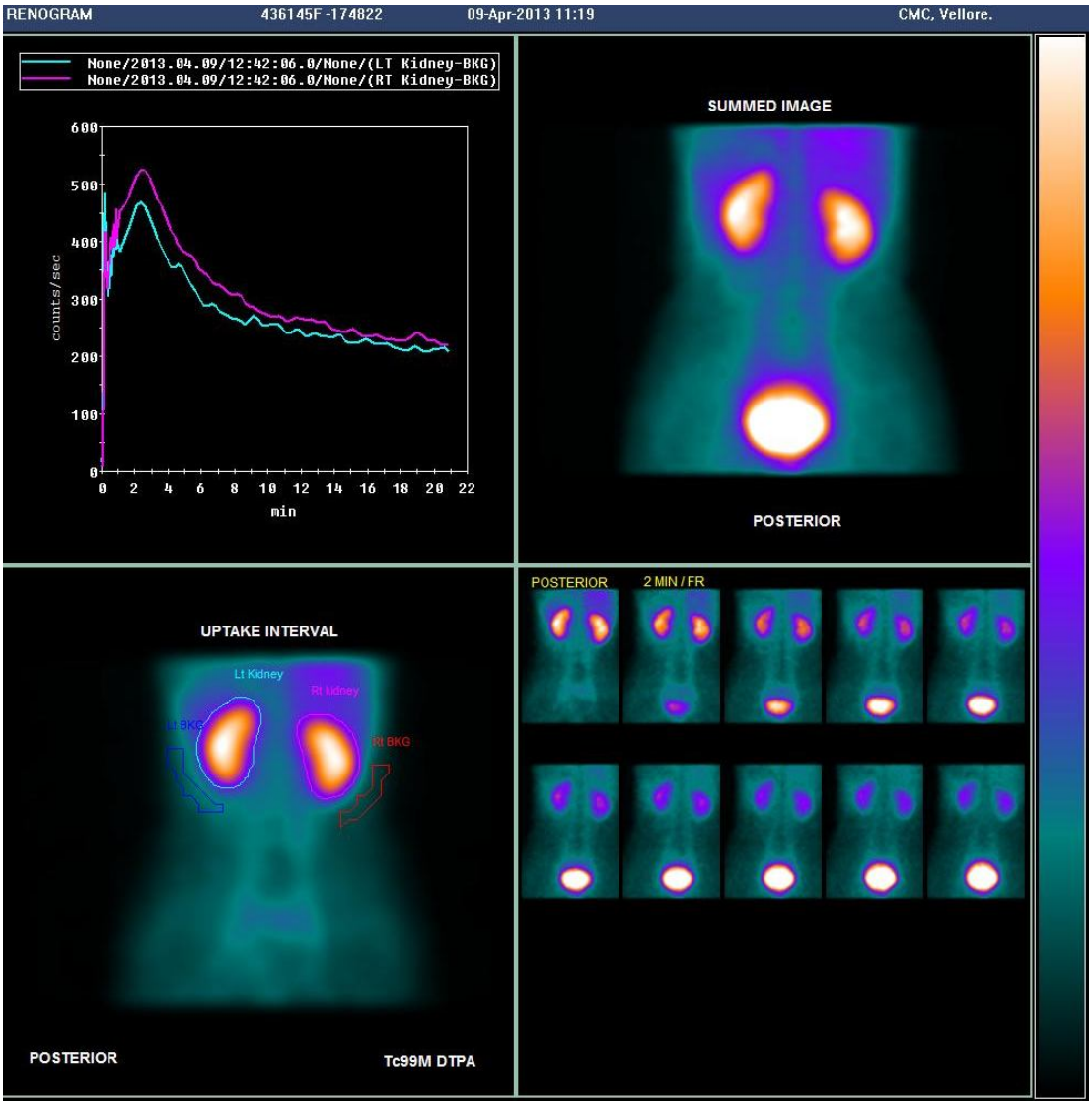

Fig 9: Tc99m DTPA renal scintigraphy showing almost equal function of both the kidneys.

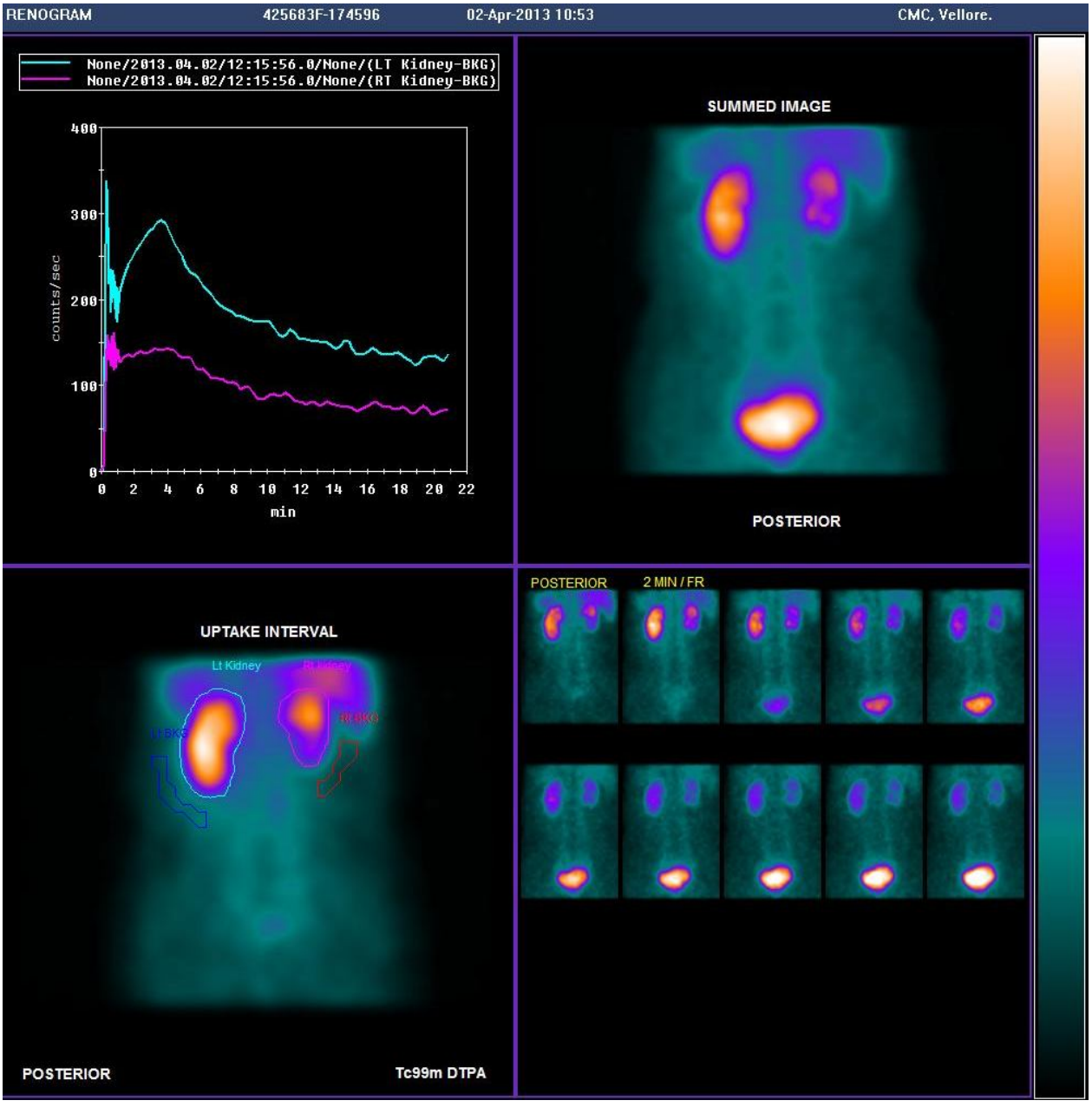

Fig 10: Tc99m DTPA renal scintigraphy shows a dominant left kidney. The relative functional difference between both the kidneys was more than 20%.

INSTITUTIONAL REVIEW BOARD APPROVAL AND FUNDING :

Institutional review board (IRB) approval was obtained prior to the commencement of the Study and the need for informed consent from the patients were waived.

STATISTICAL ANALYSIS:

Statistical analyses were performed using SPSS software version 16. For each patient, CT based split renal function estimation was compared to Tc99m DTPA renal scintigraphy results using Intra class correlation test and Pearson's correlation coefficients.Interpretation of *r* values: $r<0.25$ indicates low correlation, $0.25<r<0.5$ indicates moderate correlation, $0.5<r<0.75$ Indicates strong correlation, and $r>0.75$ indicates excellent correlation.

P <0.05 was considered significant.

Bland-Altman plots were drawn to analyze agreement between each CT method and nuclear renal scintigraphy.

Box plots were drawn for time taken for each CT method to compare ease of methods and practicality.

SAMPLE SIZE

Sample size was calculated based on the correlation coefficient (r) reported in a previous study * (Soga et al). Assuming correlation coefficient to be 0.75, with a precision of +/- 0.2 and power of 80% and a syntax level of 5%, a sample size of 65 was required.

RESULTS AND ANALYSIS

Demographic results:

SEX

	Frequency	Percent	Valid Percent	Cumulative Percent
Male	18	29.0	29.0	29.0
Female	44	71.0	71.0	100.0
Total	62	100.0	100.0	

AGE

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	62	20	59	42.00	9.962

	Frequency	Percent	Valid Percent	Cumulative Percent
INDIA	46	74.2	74.2	74.2
Bhutan	13	21.0	21.0	95.2
Bangla	2	3.2	3.2	98.4
Nepal	1	1.6	1.6	100.0
Total	62	100.0	100.0	

The mean age of the study population was 42 years with a range of 20-59 years.

Of the 62 voluntary kidney donors in our study 18 were males and 44 were females with a percentage of 29 and 71% respectively.

Majority of these patients were from India (74.2%) followed by 21% from Bhutan. Of these patients from India a vast majority were from the eastern and north eastern parts of the country.

Pearson's Correlations						
		RRV_RK	RAC_RK	RMEV_RK	RPA_RK	SCIN_RK
RRV_RK	Pearson Correlation	1	.976**	.676**	.587**	.757**
	Sig. (2-tailed)		.000	.000	.000	.000
	N	59	59	58	57	59
RAC_RK	Pearson Correlation	.976**	1	.660**	.598**	.742**
	Sig. (2-tailed)	.000		.000	.000	.000
	N	59	59	58	57	59
RMEV_RK	Pearson Correlation	.676**	.660**	1	.673**	.794**
	Sig. (2-tailed)	.000	.000		.000	.000
	N	58	58	61	60	61
RPA_RK	Pearson Correlation	.587**	.598**	.673**	1	.581**
	Sig. (2-tailed)	.000	.000	.000		.000
	N	57	57	60	60	60
SCIN_RK	Pearson Correlation	.757**	.742**	.794**	.581**	1
	Sig. (2-tailed)	.000	.000	.000	.000	
	N	59	59	61	60	62
**. Correlation is significant at the 0.01 level (2-tailed).						

Fig 11: Table showing Pearson's correlation of each CT method with the reference standard Tc99m DTPA renal scintigraphy and also amongst each other.

Mean Standard deviation of Right kidney for each method:

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
RRV_RK	59	27.0	61.5	49.776	4.4689
RAC_RK	59	25.7	61.5	49.832	4.8602
RMEV_RK	61	28.1	61.3	48.785	5.0547
RPA_RK	60	30.3	65.9	49.260	5.0378
SCIN_RK	62	34.0	62.0	51.194	4.0925
Valid N	57				

Mean and Standard deviation of Left kidney for each method:

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
RRV_LK	59	38.5	73.0	50.224	4.4689
RAC_LK	59	38.5	74.3	50.168	4.8602
RMEV_LK	61	38.7	71.9	51.215	5.0547
RPA_LK	60	34.1	69.7	50.740	5.0378
SCIN_LK	62	38.0	66.0	48.806	4.0925
Valid N	57				

Scatter plot of different methods with scintigraphy (Right):

METHOD 1: SEMI-AUTOMATED RENAL VOLUME:

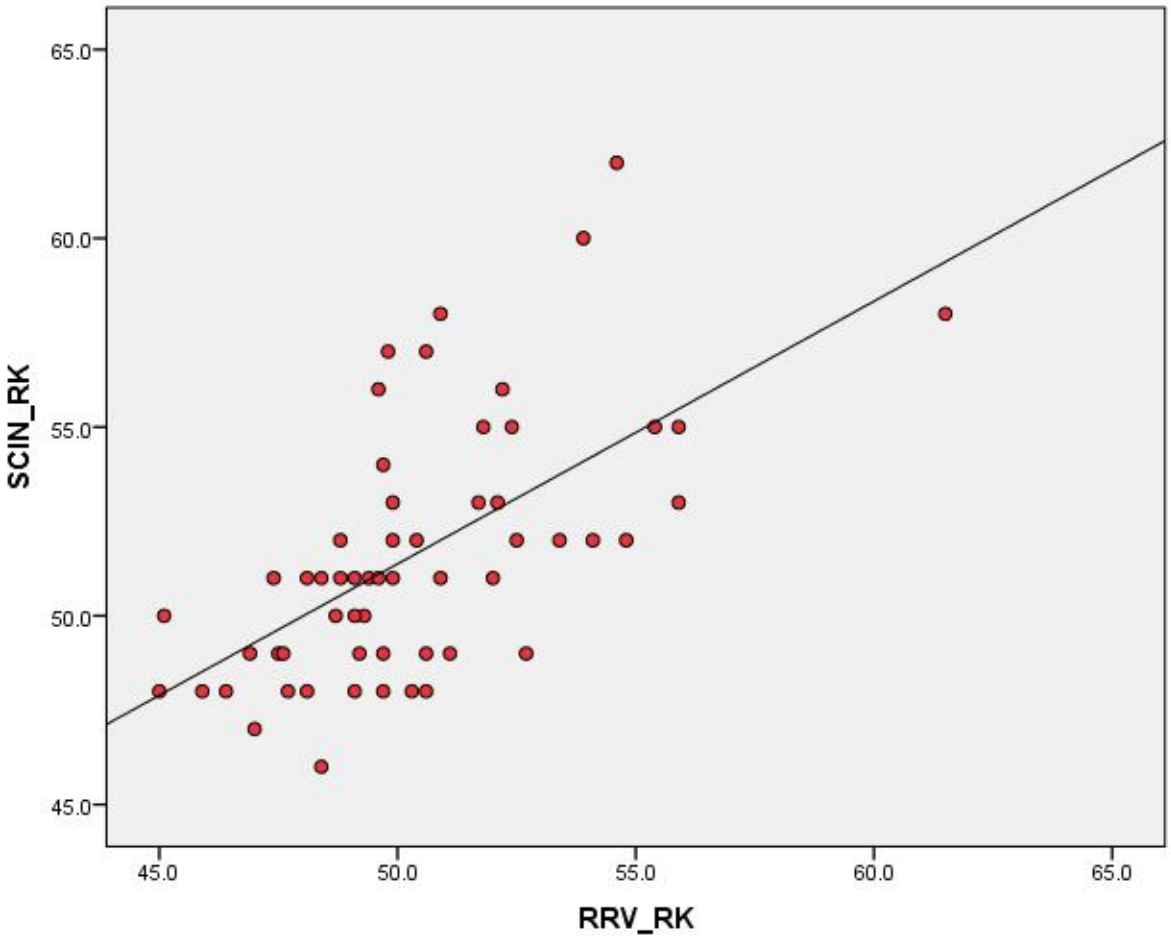

Fig 12: Correlation between Relative Renal Volume method and Tc99m DTPA renal scintigraphy (N-59, r- 0.757 and $p < 0.001$).

METHOD 2: ATTENUATION CAPACITY

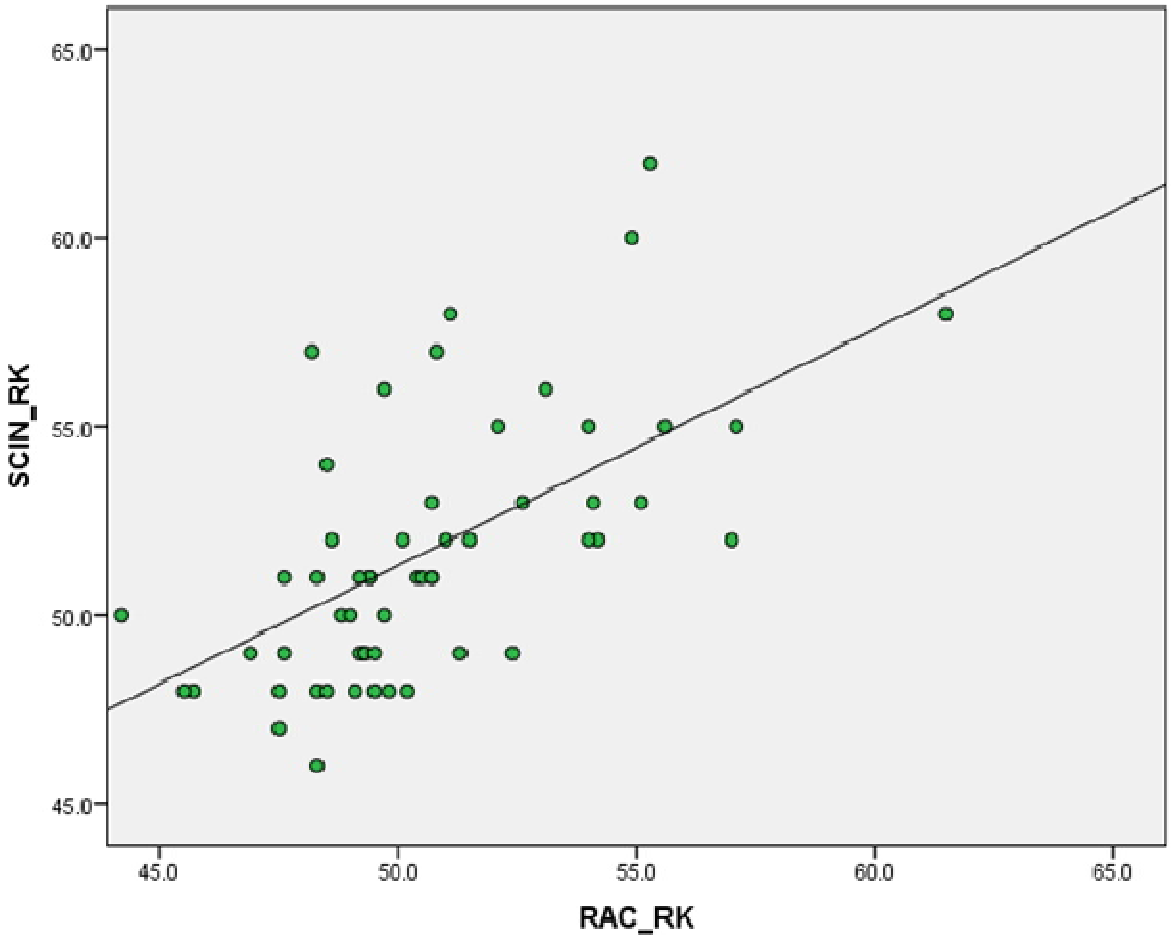

Fig 13: Correlation between Relative Renal Attenuation Capacity method and Tc99m DTPA renal scintigraphy (N-59, r- 0.742 and $p < 0.001$).

METHOD 3: MODIFIED ELLIPSOID VOLUME

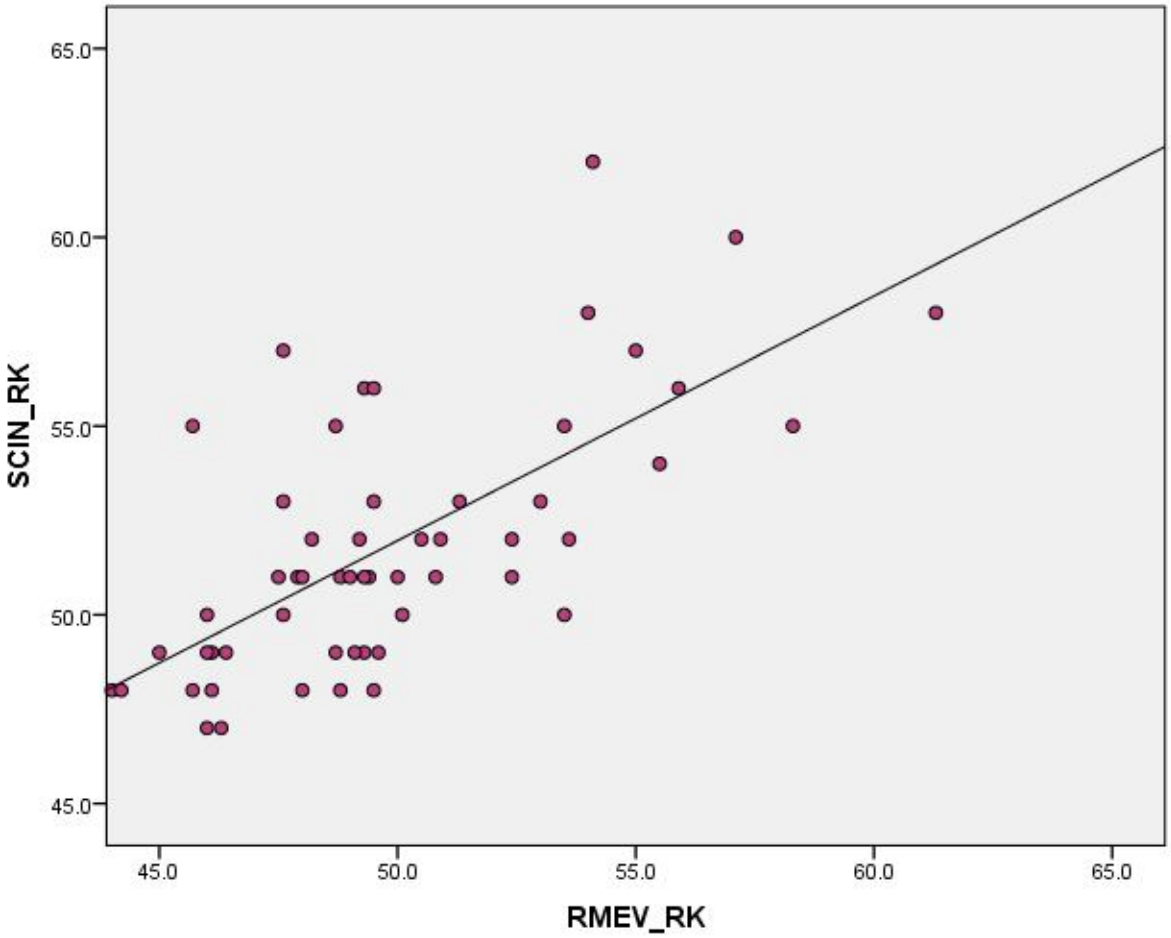

Fig 14: Correlation between Relative Modified Ellipsoid method and Tc99m DTPA renal scintigraphy (N-58, r- 0.794 and $p < 0.001$).

METHOD 4: PARENCHYMA AREA

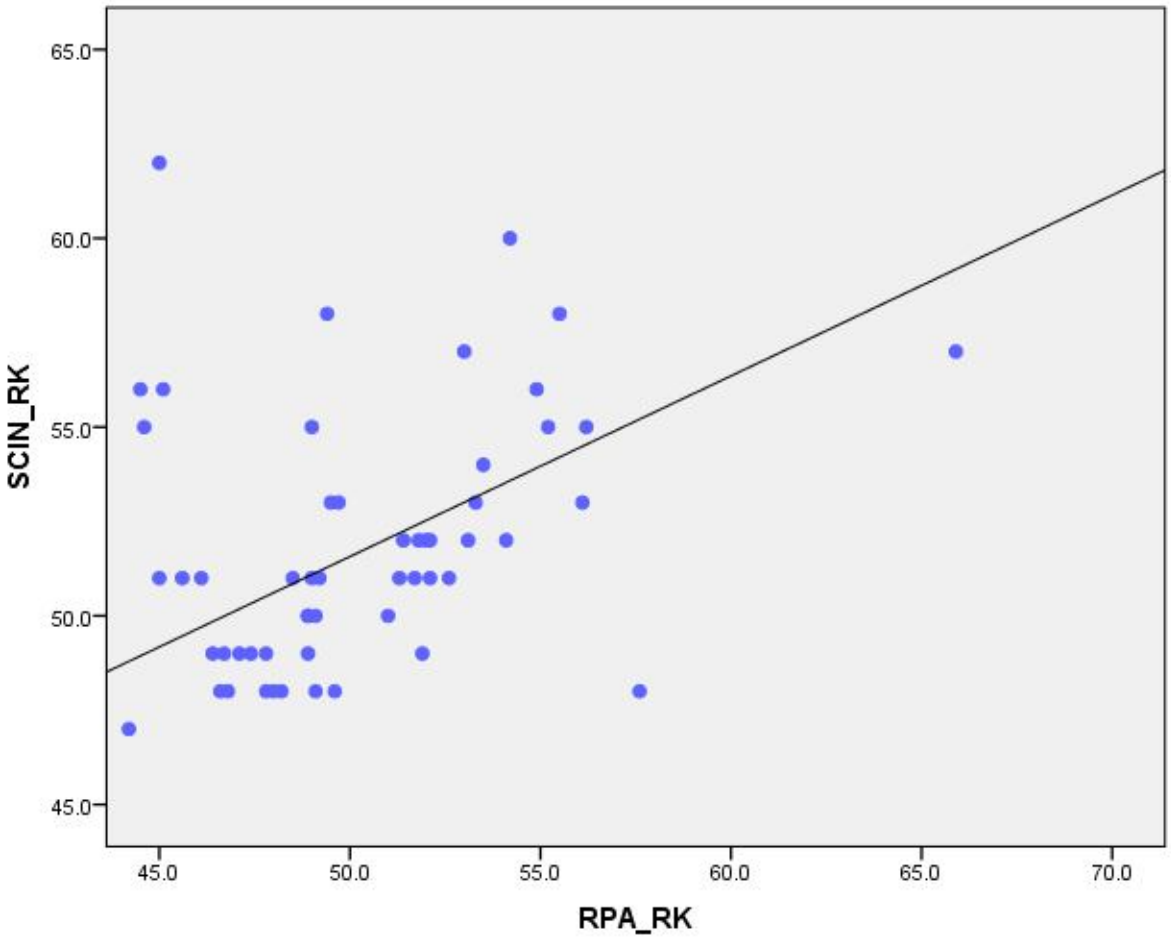

Fig 15: Correlation between Relative Parenchymal Area method and Tc99m DTPA renal scintigraphy (N-57, r- 0.58 and $p < 0.001$).

METHOD 1: SEMI-AUTOMATED RENAL VOLUME:

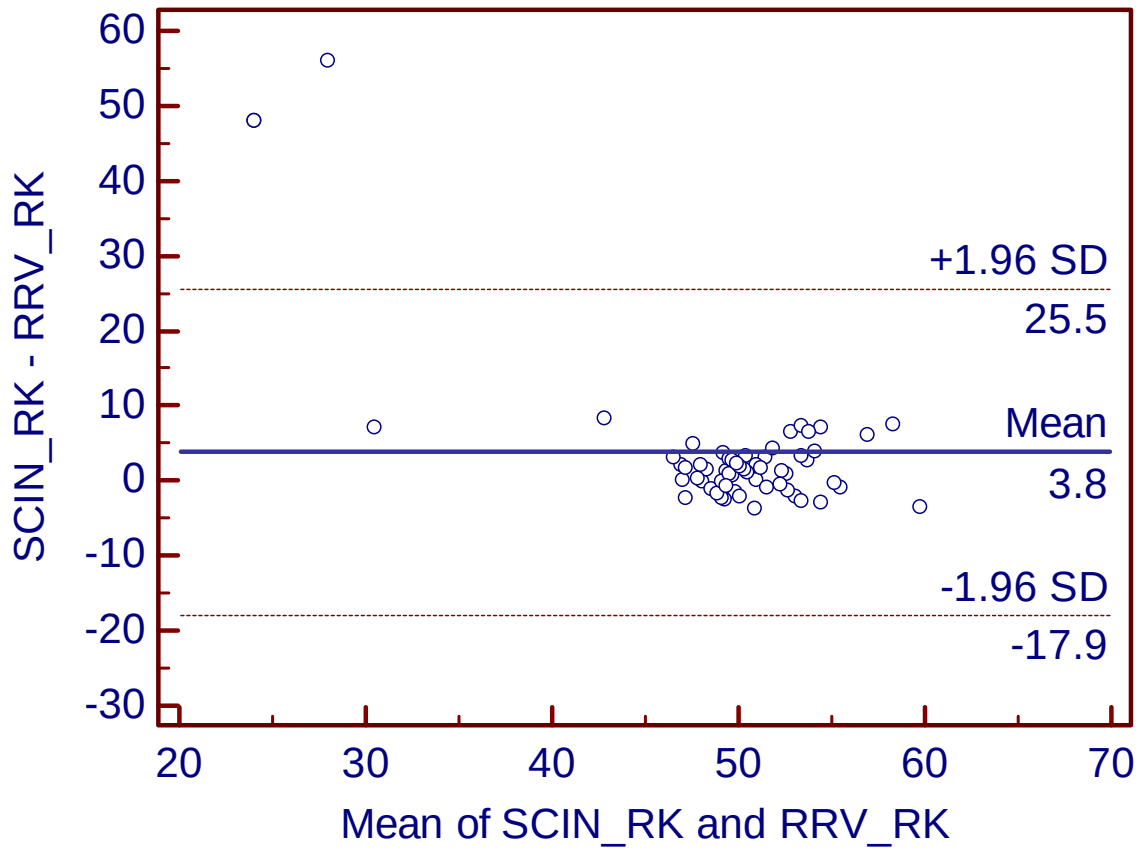

Fig 16: Differences between Relative Renal Volume Method and Tc99m DTPA renal scintigraphy based on Bland-Altman plot. The central continuous horizontal blue line represents the mean difference whereas the area between the two interrupted brown lines represents the area of 95% agreement limit (0.76).

METHOD 2: ATTENUATION CAPACITY

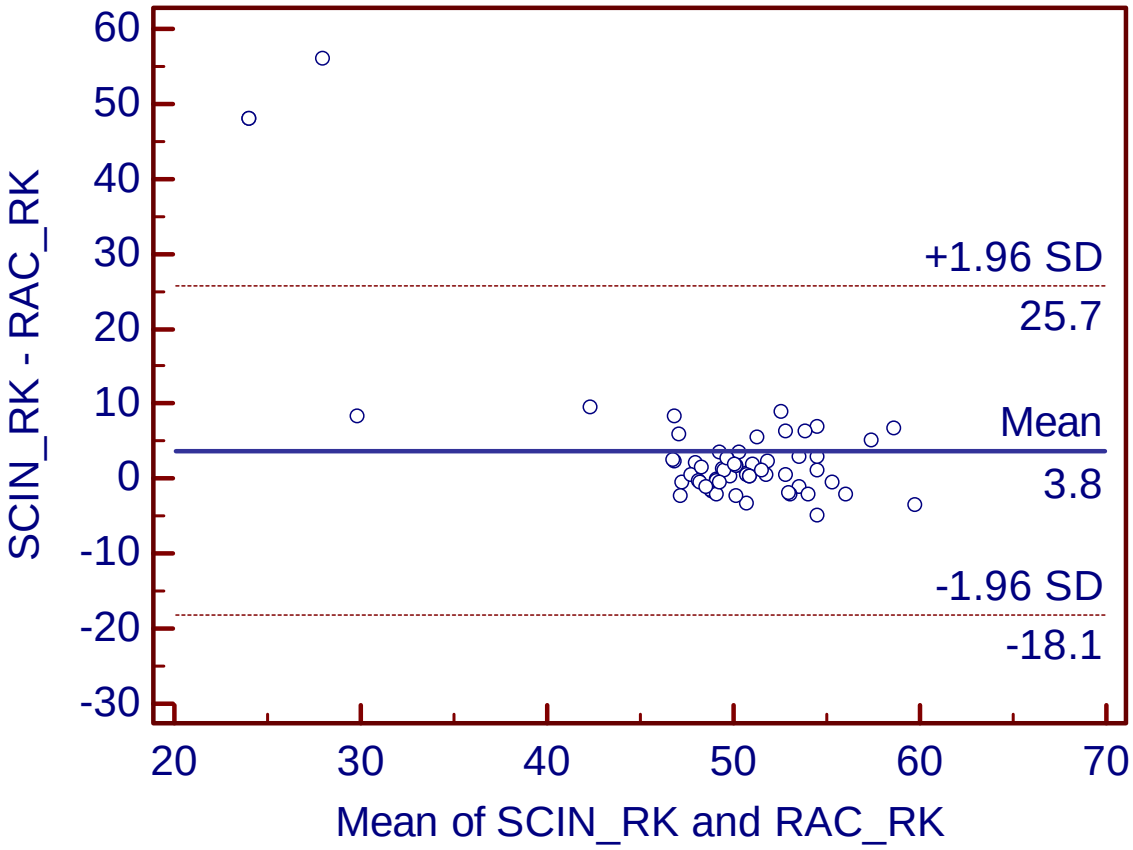

Fig 17: Differences between Relative Mean Attenuation Capacity Method and Tc99m DTPA renal scintigraphy based on Bland-Altman plot. The central continuous horizontal blue line represents the mean difference whereas the area between the two interrupted brown lines represents the area of 95% agreement limit (0.84).

METHOD 3: MODIFIED ELLIPSOID VOLUME

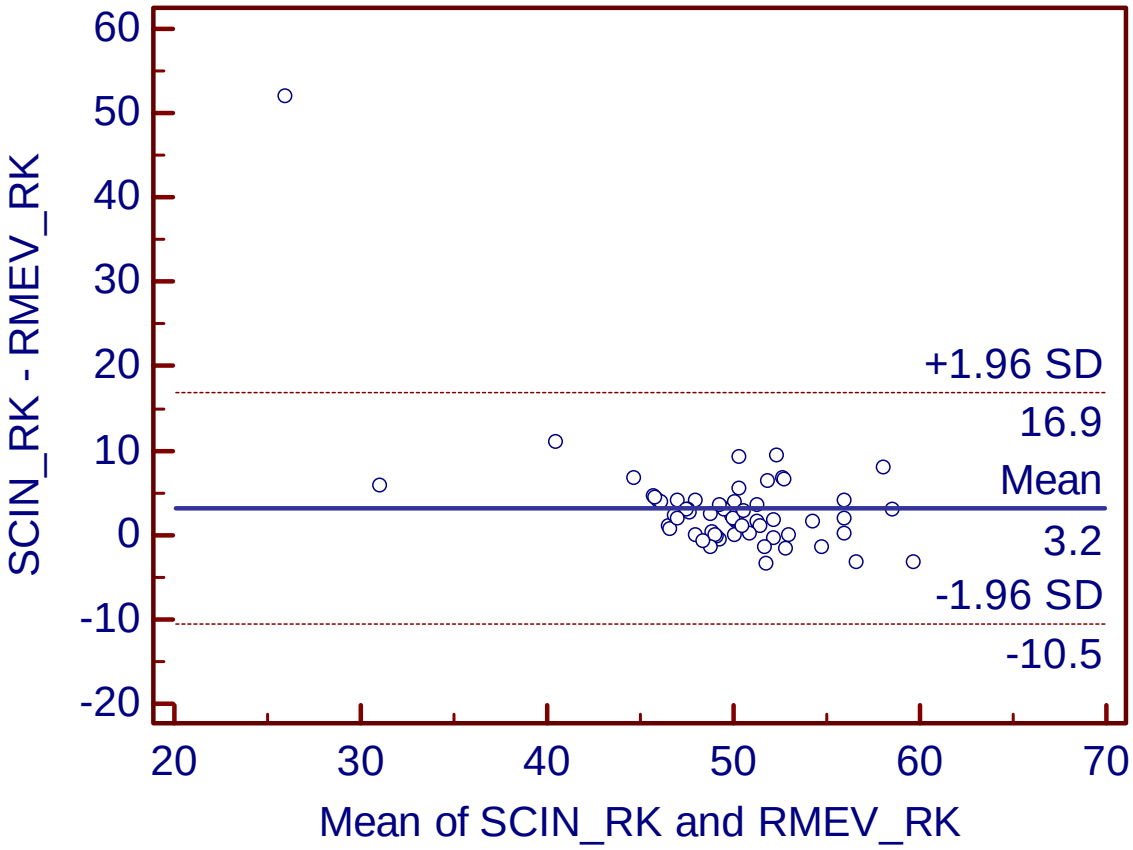

Fig 18: Differences between Relative Modified Ellipsoid Volume Method and Tc99m DTPA renal scintigraphy based on Bland-Altman plot. The central continuous horizontal blue line represents the mean difference whereas the area between the two interrupted brown lines represents the area of 95% agreement limit (0.78).

METHOD 4: PARENCHYMA AREA

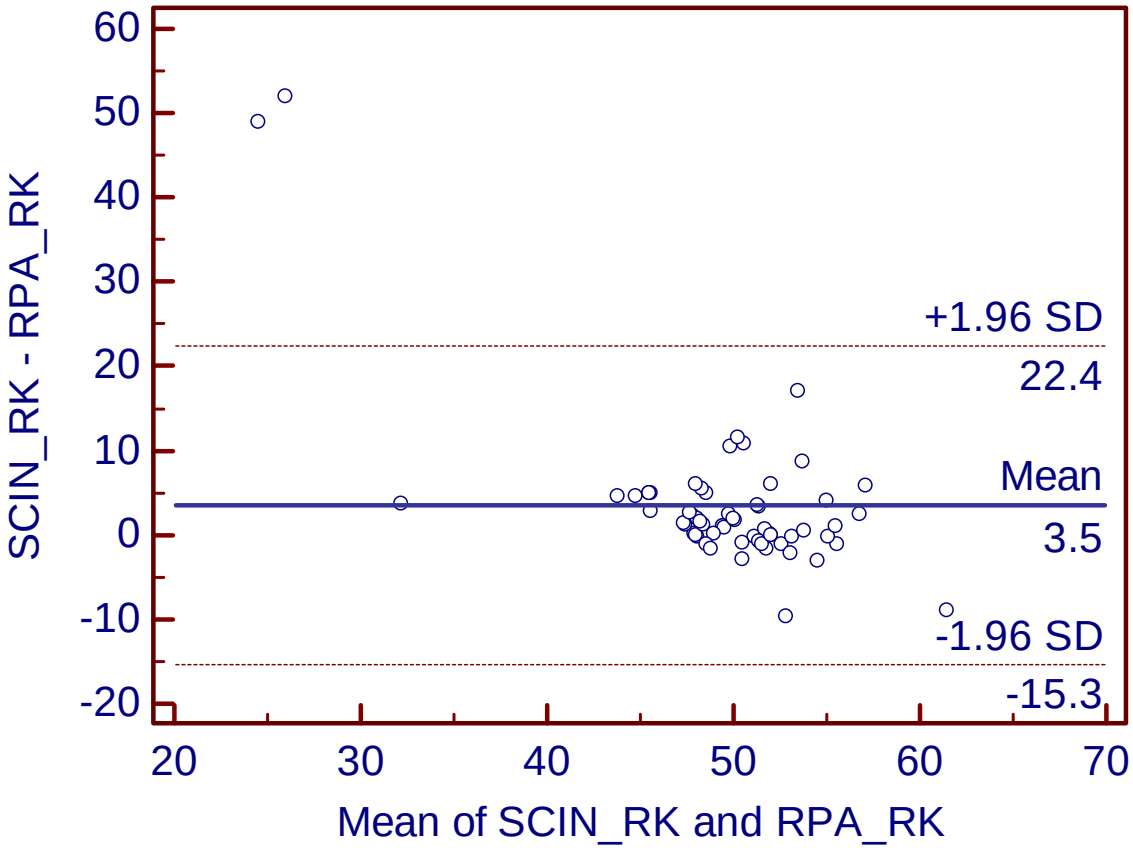

Fig 19: Differences between Relative Renal Parenchymal Area Method and Tc99m DTPA renal scintigraphy based on Bland-Altman plot. The central continuous horizontal blue line represents the mean difference whereas the area between the two interrupted brown lines represents the area of 95% agreement limit (1.08).

Methods	Bias	95% CI of bias	SD of Difference	95% CI of difference	Width of 95% CI
RRV	3.826	2.42, 5.23	3.01	1.06, 1.82	0.76
RAC	3.773	2.41, 5.24	3.30	0.97, 1.81	0.84
RMEV	3.195	2.31, 4.08	3.08	2.01, 2.79	0.78
RPA	3.523	2.30, 4.75	4.28	1.42, 2.50	1.08

Fig 20: Table summarizing Bland-Altman agreement of the CT based methods of assessing relative renal function with reference Tc99m DTPA renal scintigraphy.

METHOD 1: SEMI-AUTOMATED RENAL VOLUME:

Intraclass Correlation Coefficient

	IntraclassCorrelation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.755[a]	.619	.846	7.148	58	58	.000

Fig 21: Table showing Intra class Correlation between Relative Renal Volume method and Tc99m DTPA renal scintigraphy (N-58, r- 0.755 and $p < 0.001$).

METHOD 2: ATTENUATION CAPACITY

Intraclass Correlation Coefficient

	IntraclassCorrelation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.732[a]	.587	.831	6.454	58	58	.000

Fig 22: Table showing Intra class Correlation between Relative Mean Attenuation Capacity method and Tc99m DTPA renal scintigraphy (N-58, r- 0.732 and p < 0.001).

METHOD 3: MODIFIED ELLIPSOID VOLUME

Intraclass Correlation Coefficient

	IntraclassCorrelation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.778[a]	.655	.860	7.995	59	59	.000

Fig 23: Table showing Intra class Correlation between Relative Modified Ellipsoid method and Tc99m DTPA renal scintigraphy (N-59, r- 0.778 and p < 0.001).

METHOD 4: PARENCHYMA AREA

Intraclass Correlation Coefficient

	IntraclassCorrelation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.570[a]	.372	.719	3.654	57	57	.000

Fig 24: Table showing Intra class Correlation between Relative Parenchymal Area method and Tc99m DTPA renal scintigraphy (N-57, r- 0.57 and p < 0.001).

METHOD	INTRA CLASS CORRELATION	p VALUE	95 % CI
RRV	0.75	<0.001	0.62 to 0.85
RMAC	0.73	<0.001	0.58 to 0.83
RMEV	0.78	<0.001	0.65 to 0.86
RPA	0.57	<0.001	0.37 to 0.71

Fig 25: Table summarizing Intra class correlation of various CT based methods with reference Tc99m DTPA renal scintigraphy. The range of 95% confidence interval (CI) is also highlighted.

Box and Whisker plots

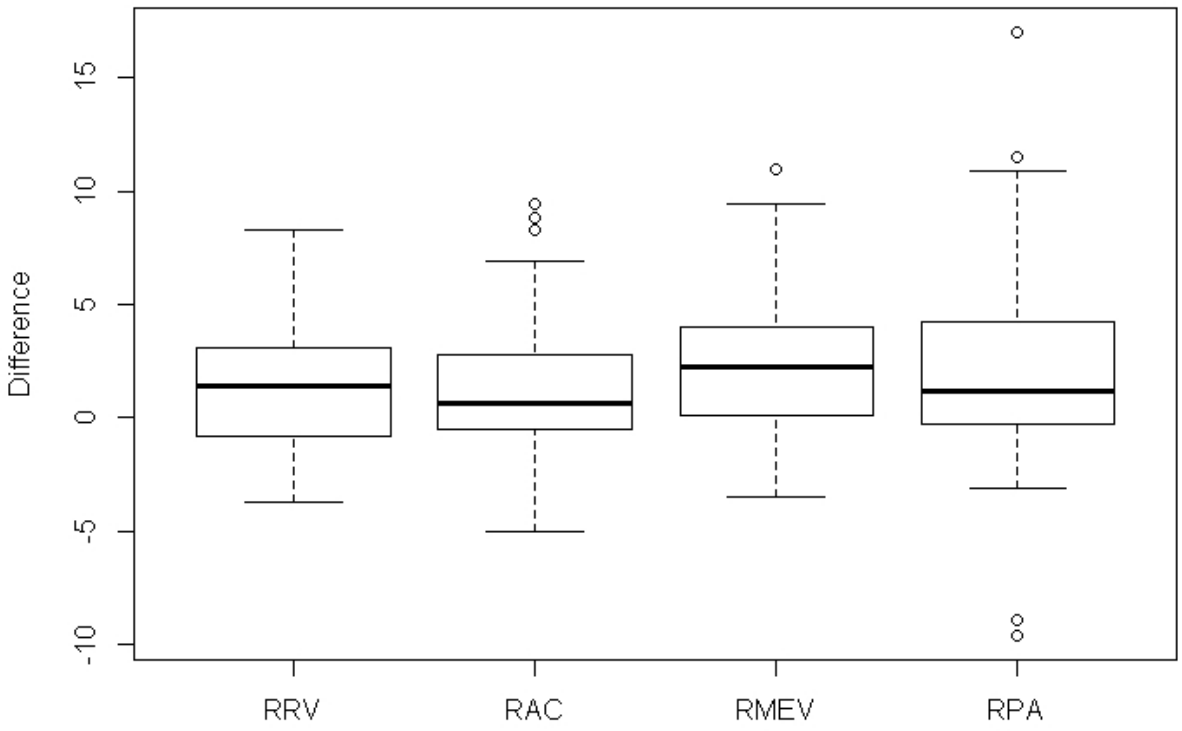

Fig 26: Box and Whisker plot of the four CT based methods of determining relative renal function with reference renal Tc99m DTPA scintigraphy. The box shows the range from the 25th percentile at the lower edge to the 75th percentile at the upper edge. The line across the box represents the median value. The number of extreme values are the highest for Relative Renal Parenchymal Area Method and least for Relative Renal Volume and Relative Modified Ellipsoid methods.

TIME TAKEN FOR EACH METHOD:

Method	Time mean	SD
RRV	19.6	4.8
RAC	20.5	5.0
RMEV	2.95	0.38
RPA	12.3	2.40

The time taken for performing methods 1 and 2 were significantly greater than the other methods as they required the principal investigator to draw dedicated ROIs on each slice with manual corrections. These methods could be performed only on a workstation and not on the PACS monitor.

Method 3 took the least time as it was technically simple and involve measurement of only 3 values for each kidney.

Method 4, though technically simple, took longer time as a total of 12 values were derived.

Both method 3 and 4 could be performed on a PACS system itself and did not need a workstation.

DISCUSSION

End stage renal disease is treated worldwide by renal transplantation. The most common form of renal donation is from live voluntary kidney donors. The preoperative imaging evaluation of these voluntary kidney donors includes CT which gives anatomical details for surgical planning. Renal scintigraphy Tc99m DTPA gives functional information and guides the surgeon regarding the choice of the renal harvest.

The ultimate aim of these imaging is to make sure that the donor does not suffer harm as a result of renal donation.In this study we have looked at the possibility of determining functional information from various CT methods and comparing those results with that of reference Tc99m DTPA renal scintigraphy.

RATIONELE BEHIND THE STUDY

Contrast enhanced CT and renal scintigraphy are part of routine work up to determine the side of nephrectomy for safe renal donation. Studies have looked at the possibility of determining relative renal function from various CT based parameters. Because of the promise shown by various CT based

methods, we decided to look at the potential role of few of these methods (which had shown promising results in recent studies) in assessing relative renal function. Also, CT is any way part of an established protocol in our institution for preoperative evaluation of renal donors and hence does not pose any additional burden to these groups of patients.

We have evaluated the diagnostic performance of four such CT based methods of determining relative renal function and also compared those results with reference standard Tc99m DTPA renal scintigraphy. This was done by determining correlation coefficients of these four CT based methods with renal scintigraphy. Various such CT based methods have shown wide variability in terms of correlation with reference standard. However a recent study by Soga et al had shown promising results for a few of these CT based methods:

1. Semi-automated volume method
2. Attenuation capacity method
3. Modified ellipsoid method
4. Parenchymal area method.

As a secondary objective we also assessed the ease of doing each of these CT based methods in terms of time taken and the technicalities involved. We also determined if CT can be the single stop imaging modality in the preoperative evaluation of renal donors.

Although a few such studies have been done in the past with promising results, no such study has been performed in the Indian subcontinent.

DISCUSSION OF RESULTS

1. Semi-automated volume method

   The results of our study show that there is excellent correlation between the results of assessing relative renal function from this method with renal scintigraphy using Tc99m DTPA.

   The Pearson's correlation coefficient of this method with that of reference standard was 0.757 which had a statistically significant $p< 0.001$.

The Pearson's correlation coefficient of this method with that of the other three CT methods were 0.976 (RAC), 0.676 (RMEV) and 0.588 (RPA) which had a statistically significant $p< 0.001$.

The Intra class correlation of this method with reference standard was 0.755 which had a statistically significant $p< 0.001$.

The Bland-Altman analysis of this method with reference standard showed the best agreement in terms of the width if CI which was 0.76 with a SD of 3.01 and a bias of 3.82.

The total number of subjects analyzed in this method was 59.

The mean time taken for performing this method was 19.6 minutes with a SD of 4.8.

2. Attenuation capacity method

The results of our study show that there is a strong correlation between the results of assessing relative renal function from this method with renal scintigraphy using Tc99m DTPA.

The Pearson's correlation coefficient of this method with that of reference standard was 0.742 which had a statistically significant $p < 0.001$.

The Pearson's correlation coefficient of this method with that of the other three CT methods were 0.976 (RRV), 0.660 (RMEV) and 0.598 (RPA) which had a statistically significant $p< 0.001$.

The Intra class correlation of this method with reference standard was 0.732 which had a statistically significant $p < 0.001$.

The Bland-Altman analysis of this method with reference standard showed good agreement in terms of the width if CI which was 0.84 with a SD of 3.30 and a bias of 3.77.

The total number of subjects analyzed in this method was 59.

The mean time taken for performing this method was 20.5 minutes with a SD of 5.

3. Modified ellipsoid method

The results of our study showed the best correlation of this method (among the other three CT methods) with renal scintigraphy using Tc99m DTPA.

The Pearson's correlation coefficient of this method with that of reference standard was excellent 0.794 which had a statistically significant $p < 0.001$.

The Pearson's correlation coefficient of this method with that of the other three CT methods were 0.676 (RRV), 0.660 (RAC) and 0.673 (RPA) which had a statistically significant $p< 0.001$.

The Intra class correlation of this method with reference standard was 0.778 which had a statistically significant $p < 0.001$.

The Bland-Altman analysis of this method with reference standard showed good agreement in terms of the width if CI which was 0.78 with a SD of 3.08 and a bias of 3.19

The total number of subjects analyzed in this method was 58.

The mean time taken for performing this method was 2.5 minutes with a SD of 0.38.

4. Parenchymal area method.

The results of our study showed the least correlation of this method (among the other three CT methods) with renal scintigraphy using Tc99m DTPA.

The Pearson's correlation coefficient of this method with that of reference standard was moderate 0.581 which had a statistically significant $p < 0.001$.

The Pearson's correlation coefficient of this method with that of the other three CT methods were 0.587 (RRV), 0.598 (RAC) and 0.673 (RPA) which had a statistically significant $p< 0.001$.

The Intra class correlation of this method with reference standard was 0.577 which had a statistically significant $p < 0.001$.

The Bland-Altman analysis of this method with reference standard showed least agreement in terms of the width if CI which was 1.08 with a SD of 4.28 and a bias of 3.52

The total number of subjects analyzed in this method was 57.

The mean time taken for performing this method was 12.5 minutes with a SD of 2.38.

SUMMARY AND CLINICAL RELAVENCE OF THE RESULTS:

Based on the results of our study comparing the four CT based methods of assessing relative renal function with the reference renal Tc99m DTPA scintigraphy, we found an excellent correlation coefficient which was statistically significant (r- 0.79, $p<0.001$) for the Relative Mean Ellipsoid Volume (RMEV) method with the reference standard.

We also found good correlation coefficients which was statistically significant for Relative Renal Volume (RRV) and Relative Renal Attenuation Capacity (RAC) methods (r-0.757 and 0.742 respectively, $p<0.001$).

We report only a moderate correlation coefficient which was statistically significant for the Relative Renal Parenchymal Area (RPA) method (r-0.58, $p<0.001$).

We also report a good agreement for the first three methods with reference renal Tc99m DTPA scintigraphy based on the Bland-AItman analysis. Based on the analysis the first three CT methods (RRV, RAC and RMEV) had width of 95% confidence interval less than 1 (0.76, 0.84 and 0.78 respectively) with a standard deviation of 3-3.3.

Among the CT based methods Relative Renal Parenchymal Area (RPA) method had the least agreement with reference renal Tc99m DTPA scintigraphy. The width of 95% confidence interval was more than 1 (1.08) with a standard deviation of 4.28.

The mean time taken was the least for method 3 or Relative Mean Ellipsoid Volume method which was approximately 3 minutes, which may be attributed to the technical simplicity of deriving only three values for each kidney (length, breadth and thickness).

The mean time taken was the maximum for methods 1 and 2 (Relative Renal Volume and Relative Renal Attenuation Capacity methods), which may be attributed to the relative technical difficulty in drawing manually corrected region of interests on each slice.

Based on these findings we infer that Method 3 or Relative Mean Ellipsoid Volume Method in terms of its highest correlation coefficient, very good agreement with the reference standard, technical simplicity and least time taken among the other CT methods is the best among the four CT methods to assess relative renal function. In view of the simplicity we recommend that this test can in fact be performed by the referring physician itself.

We also infer that methods 1 and 2 (Relative Renal Volume and Relative Renal Attenuation Capacity methods), though have a very good correlation with the reference standard are limited due to the technical complexity requiring a workstation monitor and increased time consumption. However these methods score over Relative Mean Ellipsoid Volume method in evaluating subjects with large polar cysts. Using Relative Renal Volume and Relative Renal Attenuation Capacity methods we could carefully exclude these cysts by drawing appropriate manually corrected region of interests.

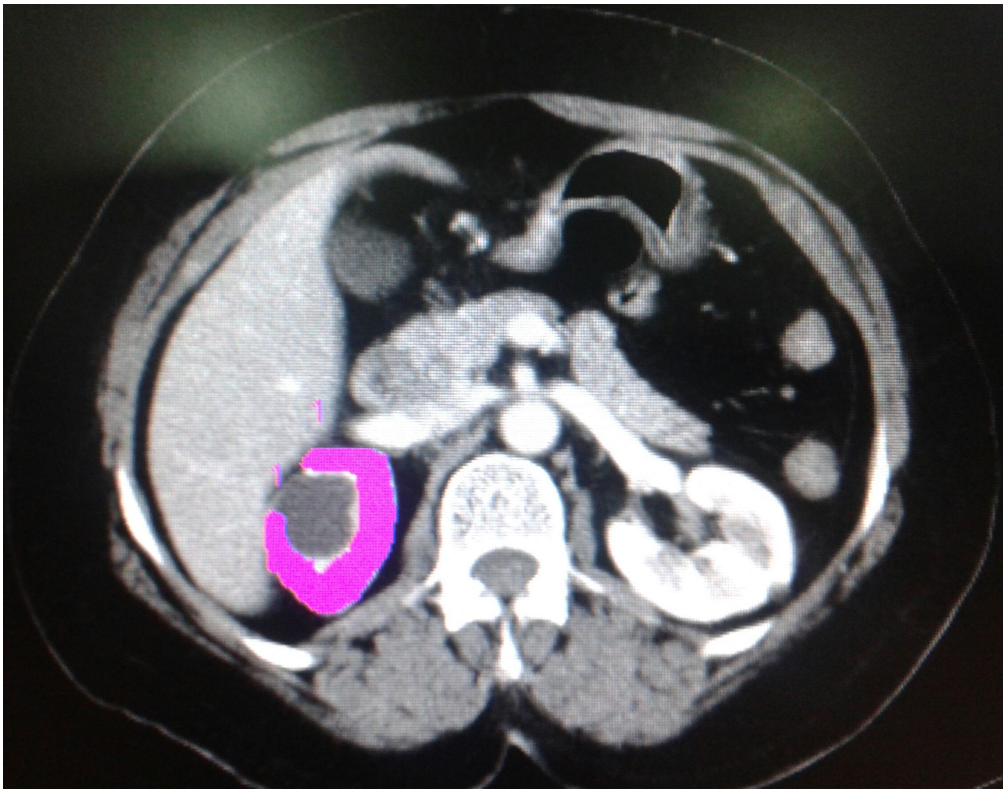

Fig 27: Intravenous contrast enhance axial CT sections of the kidneys in the venous phase shows carefull exclusion of the right renal upper polar cyst by drawing manuall corrected region of intrests in Relative Mean Attenuation Capacity method.

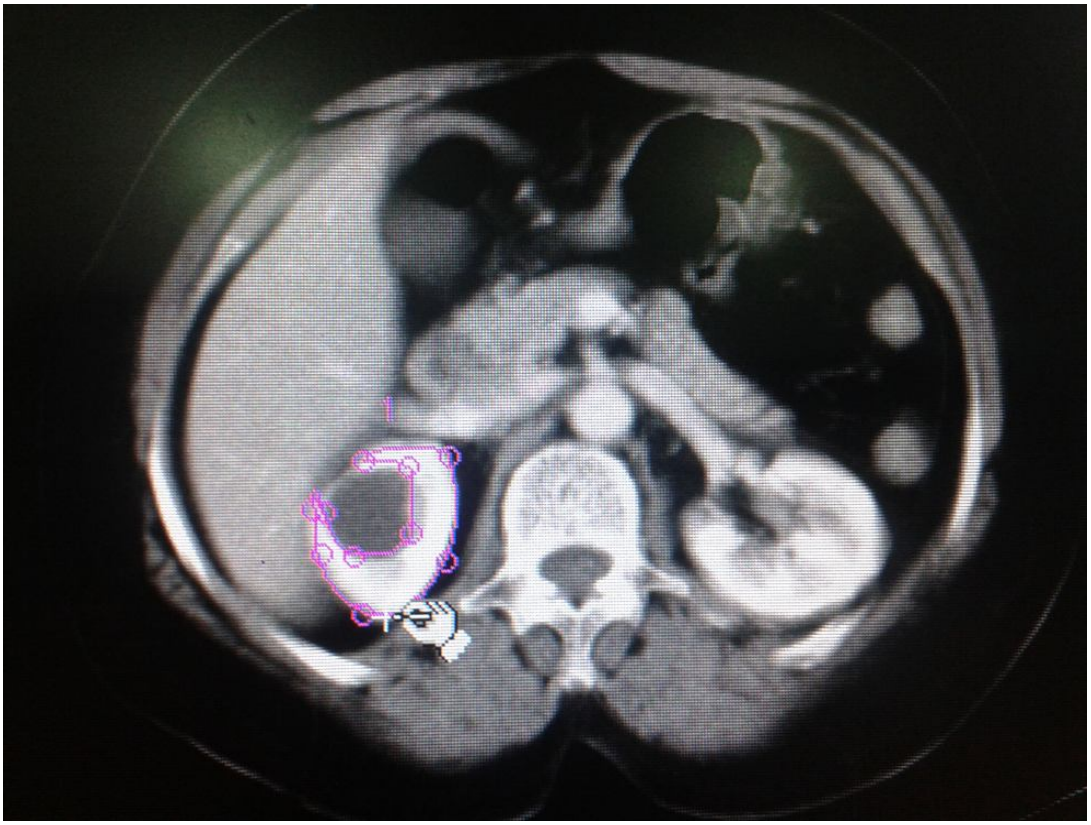

Fig 28: Intravenous contrast enhance axial CT sections of the kidneys in the venous phase shows carefull exclusion of the right renal upper polar cyst by drawing manuall corrected region of intrests in RelativeRenal Volume method.

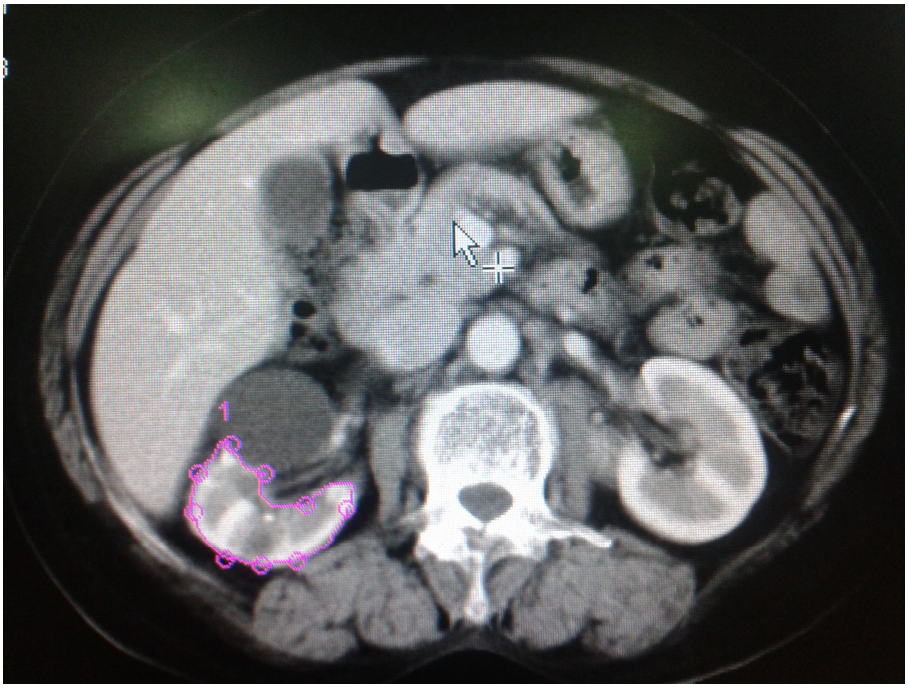

Fig 29: Intravenous contrast enhance axial CT sections of the kidneys in the venous phase shows carefull exclusion of the right renal mid polar cyst, fat and vessels by drawing manuall corrected region of intrests in Relative Renal Volume method.

Fig 30: Intravenous contrast enhanced axial CT sections of the kidneys in the venous phase shows carefull exclusion of the right renal mid polar cyst, fat and vessels by drawing manuall corrected region of intrests in Relative Mean Attenuation Capacity method.

Another interesting inference is that methods 1 and 2 (Relative Renal Volume and Relative Renal Attenuation Capacity methods), not only do they have a very good correlation with the reference standard but also have an excellent correlation (r-0.98, $p<0.001$) amongst themselves. Hence we can infer that calculation of volume alone is a good parameter in assessing relative renal function and can obviate the need for intra venous contrast enhanced scans in specific clinical scenarios.

We also report that method 4 or Relative Renal Parenchymal Area method is the least favorable in terms of lower correlation coefficient with reference standard (r-0.57, $p<0.001$), mean time of ~ 12 minutes (SD-2.4) and least agreement with reference standard as compared to the first three CT methods. This method also cannot be applied to subjects with polar cysts.

We acknowledge that the correlation coefficients for this method in our study are much lower than what was reported in some previous studies which was as high as r-0.959 (43). However that previous study included subjects with obstructive uropathy which may explain the difference.

Based on previous studies we acknowledge that the reference renal Tc99m DTPA scintigraphy has a wide variability (24). Between two repeated attempts the standard deviation of the mean difference was as high as 3.07% (48). Hence a difference of up to 7% of relative renal function does not necessarily mean significant renal functional loss (49).

DOMINANT KIDNEY

A difference of 20% is needed to label a kidney as dominant as compared to the other kidney (24, 49). Using this 20% difference as a cut off the results of the CT based methods of assessing relative function showed agreement in all subjects except one. Hence the percentage of agreement regarding the surgical decision of which kidney to harvest was as high as 98.39%.

LIMITATIONS

1. Our study was done over a short period of only ten months and hence our sample size was not large.

2. Most of the patients in our study were from the eastern parts of the Indian subcontinent and hence our results may not reflect the true demographic nature of the entire Indian subcontinent.

3. We did not countercheck the volumes determined by various CT based methods with the actual surgical renal harvests.

CONCLUSION

1. Computed tomography (CT) due to its excellent anatomical information is an established imaging modality in the pre-operative evaluation of live potential voluntary kidney donors. Intravenous non-iodinated contrast enhanced CT of the abdomen is the current radiological investigation of choice in planning for surgery in such patients.

2. When it comes to functional assessment of live potential voluntary kidney donors renal Tc99m DTPA scintigraphy is considered a reference standard though not the gold standard. A difference of up to 7% of relative renal function does not necessarily mean significant renal functional loss. A functional difference of20% is needed to label a kidney as dominant as compared to the other kidney.

3. CT based methods of assessing relative renal function is an emerging modality and a few of these methods (Relative Renal Volume, Relative Mean Attenuation Capacity and

Modified Relative Mean Ellipsoid Volume methods) are useful in assessing relative renal function prior to renal harvest surgery. The quantitative parameters assessed in these methods are the renal volume, mean attenuation capacities and mean ellipsoid volumes.

4. There is excellent correlation (r-0.79, $p<0.001$) and very good agreement of the Modified Relative Mean Ellipsoid Method with reference renal Tc99m DTPA scintigraphy. Additionally in view of technical simplicity and the least time taken among various other methods, it can be hypothesized that this method is the most practical method to be implemented in day to day practice.

5. Though Relative Renal Volume and Relative Mean Attenuation Capacity methods also show very good correlation with reference renal Tc99m DTPA scintigraphy they are time consuming and technically more difficult as compared to Modified Relative Mean Ellipsoid Method. However they are superior to Relative Mean Ellipsoid Method in the setting of evaluation of subjects with large polar cysts.

6. Relative Renal Volume and Relative Mean Attenuation Capacity methods amongst themselves show a very high correlation ($r>0.9$). Hence we can hypothesize that volume alone (though it inherently does not include perfusion and renal clearance of intravenous contrast) is sufficient to assess relative renal function in the setting of voluntary renal donation.

7. The Relative Parenchymal Area method has the least correlation coefficient and agreement with the reference standard among the other CT methods assessed in this study. Also, this method cannot be applied in the setting of a subject with large polar cysts.

8. In conclusion, with some CT based methods of assessing relative renal function in the setting of live voluntary kidney donors showing great promise in terms of reliability and applicability CT can be a one stop imaging modality and can replace renal scintigraphy in pre-operative evaluation of such patients.

In daily practice, Modified Relative Mean Ellipsoid Volume method can be used in most subjects to assess relative renal function in live voluntary potential kidney donors.

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APPENDIX 1

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PROFORMA FOR CT METHODS OF CALCULATING RELATIVE RENAL FUNCTION

Name: _____ H. No_____ Age: ____ yrs Sex: F=0/M=1

1. Renal volume (RVol):	RK _____cc	LK _____cc
2. Relative renal volume (RRV):	RK_____%	LK _____%
3. Mean attenuation (MA):	RK_____HU	LK _____HU
4. Attenuation capacity (AC):	RK_____	LK _____
5. Relative attenuation capacity (RAC):	RK_____%	LK _____%
6. Length (L):	RK_____ cm	LK _____ cm
7. Breadth (B):	RK_____ cm	LK _____ cm
8. Thickness (T):	RK_____ cm	LK _____ cm
9. Modified ellipsoid volume (MEV):	RK_____ cc	LK _____ cc
10. Relative MEV (RMEV):	RK_____ %	LK _____ %
11. Parenchymal thickness (PT):	RKUP1 _____ cm	LKUP1 _____ cm
	RKUP2 _____ cm	LKUP2 _____ cm
	RKUP3 _____ cm	LKUP3 _____ cm
	RKLP1 _____ cm	LKLP1 _____ cm
	RKLP2 _____ cm	LKLP2 _____ cm
	RKLP3 _____ cm	LKLP3 _____ cm

12. Mean PT:	RK_____ cm	LK _____ cm
13. Parenchymal area (L x Mean PT):	RK_____ cm^2	LK _____ cm^2
14. Relative PA:	RK_____ %	LK _____ %
15. Renal scintigraphy (SRFScin)	RK_____%	LK _____%

Time taken:

Method 1: semi-automated renal volumetry (RVolt): _____ min

Method 2: Attenuation capacity (ACt): _____ min

Method 3: Modified ellipsoid method (MEVt): _____ min

Method 4: Parenchymal area (PAt): _____ min